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Synthesis and Evaluation of Lipophilic BTBP Ligands for An/Ln Separations in Nuclear Waste Treatment: Effect of Alkyl Substitution on Extraction Properties and Implications for Ligand Design

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Four new 6,6'-bis(1,2,4-triazin-3-yl)-2,2'-bipyridine (BTBP) ligands containing either additional alkyl groups on the pyridine rings, or 7-membered aliphatic rings attached to the triazine rings, have been synthesized, and the effects of additional alkyl substitution in the 4- and 4'-positions of the pyridine rings on their extraction properties with Ln(III) and An(III) cations in simulated nuclear waste solutions were studied. The speciation of ligand **13** with some trivalent lanthanide nitrates was elucidated by ^{1}H NMR titrations and electrospray-ionization mass spectrometry. Whereas ligand **13** formed both 1:1 and 1:2 complexes with La(III) and Y(III), only 1:2 complexes were observed with Eu(III) and Ce(III). Quite unexpectedly, both alkyl-substituted ligands **12** and **13** showed lower solubilities in certain diluents than the non-substituted ligand CyMe$_4$-BTBP. Compared to CyMe$_4$-BTBP, alkyl-substitution was found to decrease the rates of metal ion extraction of the BTBPs in both 1-octanol and cyclohexanone. A highly efficient (D_{Am} > 10) and selective ($SF_{Am/Eu}$ > 90) extraction was observed for BTBPs **12** and **13** in cyclohexanone, and for BTBP **13** in 1-octanol in the presence of a phase-transfer agent. The implications of these results for the design of improved extractants for radioactive waste treatment are discussed.

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Introduction

One of the major goals in the treatment of nuclear waste arising from the PUREX process is the selective removal of the radiotoxic minor actinides (Am and Cm) from the lanthanides in a solvent extraction process, known as the SANEX process.[1] Once removed, the oxides of these elements may be converted by high-energy neutrons (transmutation) into less radiotoxic or non-radiotoxic elements, enabling the safer geological disposal of the remaining waste, or they may be used as fuel in their own right in the proposed Generation IV fast reactors.[2] This strategy, known as Partitioning and Transmutation, promises to reduce the environmental impact and ultimately increase the sustainability of nuclear energy.[3]

A large number of extractants has been proposed and tested in recent years for their ability to extract actinides in the presence of lanthanides from aqueous nitric acid solutions produced during the PUREX reprocessing of nuclear waste.[4] Most promising are the 2,6-bis(1,2,4-triazin-3-yl)pyridine (BTP)[5] and the 6,6'-bis(1,2,4-triazin-3-yl)-2,2'-bipyridine (BTBP)[6] ligands, and one member of the latter family (CyMe$_4$-BTBP **1**, Figure 1)[7,8] is the current benchmark ligand for the SANEX process, as demonstrated on genuine waste fuel solution.[9] The substituted aliphatic rings present in **1** are designed to confer solubility in suitable solvents such as 1-octanol, while the absence of benzylic hydrogens enhances the resistance of the ligands to radiolytic degradation caused by free-radical species.[10] Recently, it has been shown that the extraction properties of ligands such as **1** can be improved considerably if the ligand is pre-organized for metal binding with a phenanthroline moiety, which locks the ligand into the required *cis* conformation.[11]

The *tert*-butyl-substituted derivative **2**[12] (Figure 1) posesses a higher solubility than CyMe$_4$-BTBP **1** in suitable diluents such as 1-octanol and cyclohexanone,[13] although its solvent extraction kinetics are slower than those of **1**. More recently, a symmetrical BTP ligand derived from camphor has shown both improved solubility and fast extraction kinetics compared to related BTP ligands.[14] However, this ligand is susceptible to precipitate formation in contact with nitric acid solutions of high acidity. A high extractant solubility is desirable for the treatment of waste solutions containing high concentrations of metal ions, such as those produced in the PUREX process.[15] In this study, we have therefore synthesized and evaluated some lipophilic symmetrical BTBP ligands based on CyMe$_4$-BTBP **1** containing either two additional alkyl groups, or 7-membered aliphatic rings in order to determine the effects of these modifications on the solubilities and extraction properties of the ligands, and our results are reported herein.

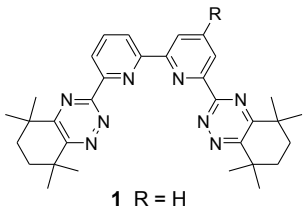
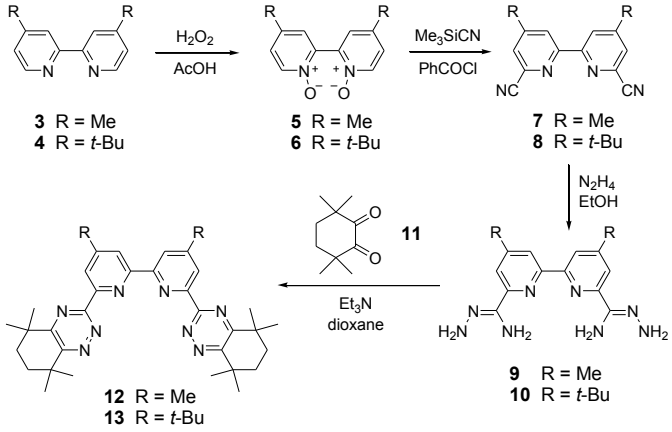


Figure 1. Structures of $CyMe_4$-BTBP **1** and MF2-BTBP **2**.

Results and Discussion

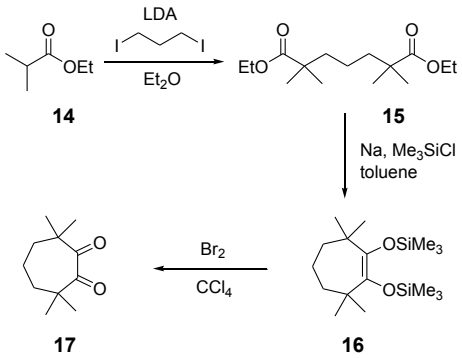
Ligand Synthesis

The 4,4'-disubstituted BTBP ligands **12** and **13** were synthesized using the same methodology previously used to synthesize $CyMe_4$-BTBP **1**.[7,8] Oxidation of the 2,2'-bipyridines **3** and **4** with hydrogen peroxide in acetic acid afforded the bis-*N*-oxides **5**[16,17] and **6**[17,18] which were converted to the dicarbonitriles **7**[17,19] and **8**[17] by a Reissert-Henze reaction with trimethylsilyl cyanide and benzoyl chloride in DCM (**CAUTION:** trimethylsilyl cyanide is a volatile hydrogen cyanide equivalent!). The dicarbonitriles **7** and **8** were treated with hydrazine hydrate in ethanol to generate the novel dicarbohydrazonamides **9** and **10** in 81 % and 79 % yields, respectively. Finally, condensation of **9** and **10** with 3,3,6,6-tetramethylcyclohexane-1,2-dione **11**[20] (which was synthesized by a modified procedure)[11,21] furnished the new 4,4'-disubstituted BTBP ligands **12** and **13** (Scheme 1).

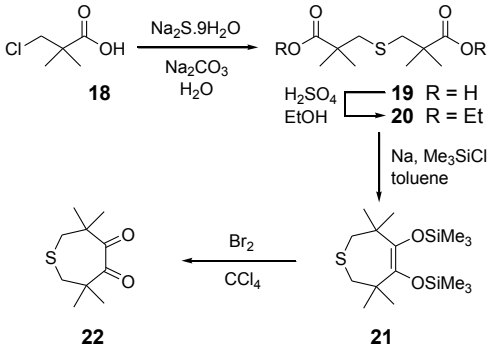


Scheme 1.

We also reasoned that a BTBP ligand containing a 7-membered aliphatic ring would also have a higher solubility than $CyMe_4$-BTBP **1** in suitable organic diluents. Consequently, we pursued the synthesis of BTBPs **24** and **25** derived from the condensation of dicarbohydrazonamide **23**[22] with the 7-membered ring diketones **17** and **22**. The known α-diketones **17**[23–25] and **22**[23,24,26] were synthesized according to literature procedures as shown in Schemes 2 and 3. The intramolecular acyloin reaction of diesters **15**[23b] and **20**[27] with sodium in the presence of chlorotrimethylsilane afforded the enediolate bis-silyl ethers **16**[23] and **21**,[23] respectively. These products were then oxidized to the corresponding α-diketones **17** and **22** using bromine in CCl_4.

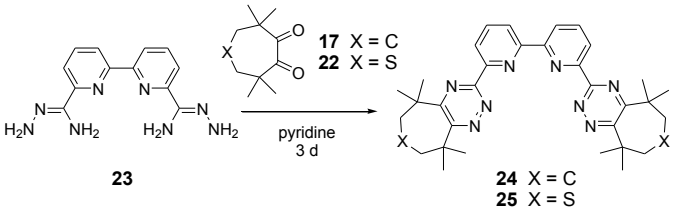


Scheme 2.



Scheme 3.

The condensation reaction of dicarbohydrazonamide **23** with each of the diketones **17** and **22** failed to generate the corresponding BTBP ligands **24** and **25** in a range of different solvents (THF, dioxane, EtOH, toluene, dibutyl ether, DMSO), and starting materials were recovered in each case. Eventually, we found that the reactions proceeded in pyridine after refluxing for 3 days (Scheme 4). We attribute the reduced reactivity of the 7-membered ring diketones **17** and **22** in these reactions to the differences in the O=C–C=O dihedral angles between these diketones and the more reactive 6-membered ring diketone **11**.[25b] Examination of the ^{1}H NMR spectrum of the crude products showed the expected resonances of the BTBPs in addition to at least one other product in each case that could not be identified. Unfortunately, all attempts at further purification of the crude BTBPs **24** and **25** failed (recrystallization, chromatography, trituration) and consequently, pure samples of these ligands could not be obtained for evaluation of their solvent extraction properties.



Scheme 4.

It is also known that the BTP and BTBP ligands extract a number of fission products such as Mo, Zr, Ni, Pd and Pb into the organic phase in addition to Am(III) and Cm(III).[5g] The presence of these metals in sufficiently high concentrations can interfere with the extraction of Am(III) in an separation process by

sequestering the extractant. We therefore synthesized a Pd(II) complex of BTBP **13** using a procedure reported by us previously[28] in order to characterize the type of species that could be involved in the extraction of Pd(II). The 1:1 and 1:2 complexes of related BTBPs with Ni(II) have been reported previously.[29] The 1:1 Pd(II) complex of BTBP **13** was synthesized by treatment of **13** with $Pd(OAc)_2$ in MeOH at reflux, followed by anion metathesis with saturated methanolic ammonium hexafluorophosphate. The ^{1}H NMR data for the complex were consistent with the formation of a single symmetrical species. However, attempts to obtain suitable crystals for X-ray diffraction analysis were unsuccessful.

NMR Titrations with Lanthanide Salts

NMR titrations of ligands with metal salts are a useful tool for probing the binding properties of ligands in solution and determining the stoichiometries of their complexes.[30] The solution phase speciation of BTBP **13** with some trivalent lanthanide nitrate salts was thus studied by ^{1}H NMR titrations in order to determine the stoichiometries of the complexes formed. The progressive addition of lanthanide nitrate salts (in CD_3CN) in aliquots of 0.1 equivalents to a solution of **13** in $CDCl_3$ led to the gradual disappearance of the resonances from the free ligand and the appearance of resonances corresponding to the metal complexes. Integration of a given resonance for each species gives the relative amounts of the species present at different metal:ligand ratios. In the case of lanthanum, both 1:1 and 1:2 complexes are formed during the course of the titration (see Supporting Information). The 1:1 species is the major species present at high metal:ligand ratios while the 1:2 species dominates if the metal:ligand ratio is 0.7 or less. However, even after 1.3 equivalents of metal have been added, some 1:2 complex still remains. In a previous study on BTP ligands, lanthanum complexes of 1:1, 1:2 and 1:3 stoichiometries were found to be in equilibrium.[10] The normalized species distribution curve for the titration of lanthanum with **13** is presented in Figure 2. An enlargement of the aromatic region of the stack plot is shown in the Supporting Information.

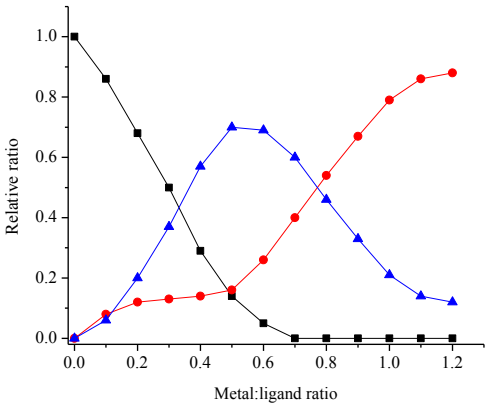


Figure 2. ^{1}H NMR titration of BTBP **13** with $La(NO_3)_3$ in $CDCl_3/CD_3CN$ (■ = free ligand, ● = 1:1 complex, ▲ = 1:2 complex).

In the titrations of **13** with europium and cerium nitrates, the progressive formation of only a single metal complex is observed. Coordination of **13** to the paramagnetic Eu(III) ion causes a pronounced upfield shift to ca. 6.2 ppm of one of the resonances for the aromatic protons. The disappearance of the free ligand resonances once 0.7 equivalents of europium, or 0.8 equivalents of cerium have been added, suggests that a 1:2 complex is formed, rather than a 1:1 complex. However, at a metal:ligand ratio of 0.5, the ratio of free ligand to metal complex is close to 1:1 (see Supporting Information). Assuming the formation of 1:2 complexes, the observation of free ligand resonances after 0.5 equivalents of metal have been added indicates that the complexation reaction does not reach completion, and is effectively driven to completion by the further addition of the lanthanide salts. A stack plot for the titration of **13** with $Eu(NO_3)_3$ is shown in Figure 3.

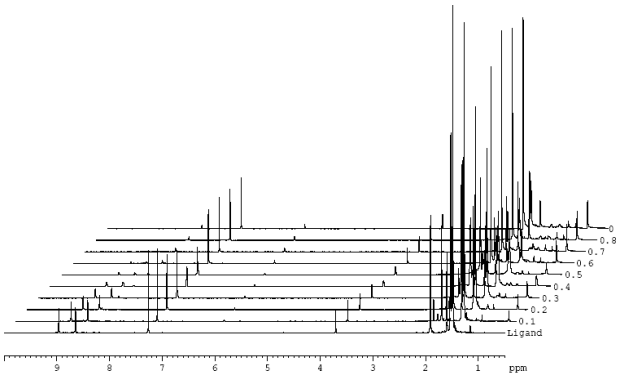


Figure 3. NMR stack plot corresponding to the titration of BTBP **13** with $Eu(NO_3)_3$. First (bottom) spectrum = spectrum of free ligand. Each subsequent spectrum corresponds to the addition of 0.1 eq. of $Eu(NO_3)_3$.

As was the case with lanthanum, both 1:1 and 1:2 species were observed in the titration of **13** with yttrium (Figure 4). However, in contrast to lanthanum, the 1:1 species is more prevalent even at low metal:ligand ratios. Whereas the 1:1 complex of **13** with lanthanum becomes the major solution species after the addition of 0.8 equivalents of metal salt, the 1:1 complex of **13** with yttrium is the major species present after only 0.4 equivalents of metal salt have been added. It is notable that the bis-complex of **13** with yttrium is less able than that of lanthanum to dissociate and form 1:1 complexes towards the end of the titration, and the ratio of 1:1 and 1:2 complexes remains largely unaltered despite the further addition of metal salt solution. This may reflect the greater polarizing ability of the Y(III) cation compared to La(III). The stoichiometries of the metal complexes formed at the end of the titrations of **13** with La(III), Eu(III) and Ce(III) were verified by electrospray-ionization mass spectrometry (see Supporting Information). Mass peaks were observed for the 1:2 complexes $[M(\mathbf{13})_2(NO_3)]^{2+}$ in each case.[31] The isotope distribution patterns of the mass peaks were in excellent agreement with those calculated from computer simulation. Despite repeated attempts, efforts to elucidate the crystal structures of the lanthanide complexes of **13** by X-ray crystallography were unsuccessful.

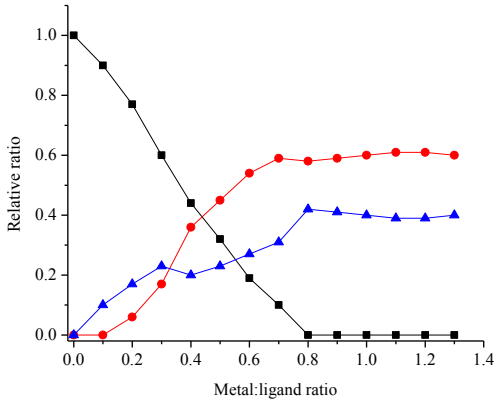


Figure 4. ^{1}H NMR titration of BTBP **13** with $Y(NO_3)_3$ in $CDCl_3/CD_3CN$ (■ = free ligand, ● = 1:1 complex, ▲ = 1:2 complex).

The data collected from the NMR titrations of **13** with lanthanide nitrate salts was used to develop a model for the complexation reactions from which the preliminary stability constants of the complexes were obtained (see Supporting Information for details).[32] The preliminary calculated equilibrium stability constants for the complexes formed between **13** and La(III), Y(III), Eu(III) and Ce(III) are presented in Table 1.

Table 1. Calculated stability constants of the 1:1 (*K1*) and 1:2 (*K2*) complexes of **13** with Ln(III)

System	1:1 complex *K1* [L/mol]	1:2 complex *K2* [L/mol]^2
Ce - BTBP	n/a[a]	1.44 E+16 ± 2.08 E+15
Eu - BTBP	n/a[a]	1.42 E+16 ± 1.52 E+15
Y - BTBP	6.12 E+13 ± 2.26 E+13	6.12 E+21 ± 2.48 E+21
La - BTBP	6.12 E+13 ± 2.32 E+13	6.12 E+21 ± 2.63 E+21

[a] 1:1 complex not observed

Solvent Extraction Properties

The novel BTBP ligands **12** and **13** were evaluated for their ability to extract and separate Am(III) from Eu(III) from aqueous nitric acid solutions into suitable organic diluents. The crude BTBP ligands **24** and **25** were not evaluated owing to the difficulties encountered in their purification. The approximate solubilities of the ligands **12** and **13** in these diluents were first determined and are shown in Table 2. Quite unexpectedly, both ligands **12** and **13** showed slightly lower solubilities than $CyMe_4$-BTBP **1** and BTBP **2** in both 1-octanol and cyclohexanone,[13] despite the presence of the additional alkyl groups. A higher solubility of the ligands was anticipated in these diluents. However, as shown by Ekberg *et al*, the non-symmetrical BTBP **2** posesses a far higher solubility than the symmetrical $CyMe_4$-BTBP **1** due to its higher entropy of dissolution.[13] In the symmetrical BTBP ligands **12** and **13**, this entropy effect will be lost resulting in a lower solubility compared to **2**. It thus appears that alkyl substitution in a non-symmetrical BTBP ligand such as **2** is the most promising method of increasing its solubility. Both ligands **12** and **13** were more soluble in cyclohexanone than in 1-octanol, although paradoxically the solubility of **12** was slightly higher than that of **13** in both of these diluents. Neither ligand showed any appreciable solubility in dodecane. For comparison purposes, 5 mM solutions of each ligand in each of the diluents were used in the initial extraction experiments (for **13** in 1-octanol, a concentration of 4.8 mM was used).

Table 2. Approximate solubilities of BTBP ligands **12** and **13**.

Diluent	BTBP **12**	BTBP **13**
1-octanol	6 – 8 mM	4.8 – 10 mM
cyclohexanone	17 – 19 mM	14 – 17 mM
3-methylcyclohexanone	6 – 8 mM	n/a[a]

[a] Not determined

The distribution ratios for Am(III) and Eu(III) (D_{Am} and D_{Eu}), and the separation factors for americium over europium ($SF_{Am/Eu}$) for the dimethyl-substituted BTBP **12** dissolved in 1-octanol as a function of the nitric acid concentration of the aqueous phase are shown in Figure 5. As shown, a reasonable selectivity is observed for Am(III) over Eu(III), particularly at higher acidities ($SF_{Am/Eu}$ = 26 at 4 M HNO_3). The *D* values for both Am(III) and Eu(III) increase with increasing nitric acid concentration of the aqueous phase, in agreement with previous studies on the BTBP ligands. Similar results were observed for the more lipophilic di-*tert*-butyl-substituted BTBP **13** in octanol (Figure 6). A lower maximum separation factor was observed in this case ($SF_{Am/Eu}$ = 14.8 at 4 M HNO_3). It is notable that, for both ligands the *D* values remain below 1, despite using a long phase contact time of 6 hours in each case. In contrast, *D* values of up to 10 are observed for $CyMe_4$-BTBP **1** in 1-octanol (10 mmolar) within 1 hour of phase contact,[7] although a faster shaking device was used in that case. Since the extracted complexes formed by ligands **12** and **13** would be expected to be more lipophilic than those formed by either **1** or **2**, we wondered if the lower *D* values observed might be due to slower extraction kinetics.

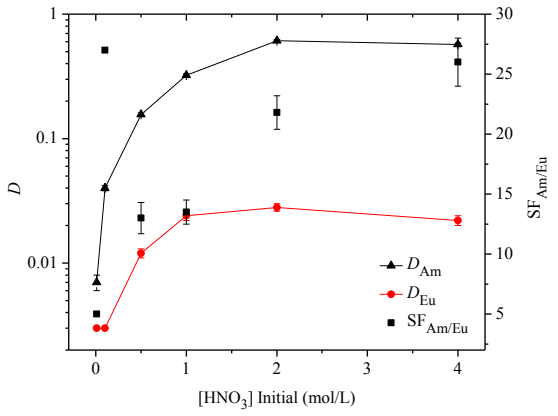


Figure 5. Extraction of Am(III) and Eu(III) as a function of $[HNO_3]$ for BTBP **12** in 1-octanol (5 mM) at 25 °C, non-thermostatted (▲ = D_{Am}, ● = D_{Eu}, ■ = $SF_{Am/Eu}$, contact time = 6 hours).

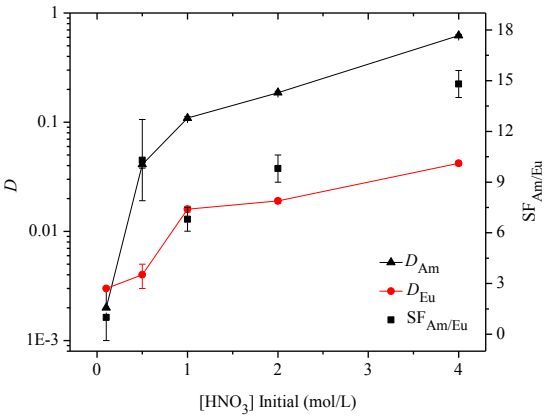


Figure 6. Extraction of Am(III) and Eu(III) as a function of [HNO_3] for BTBP **13** in 1-octanol (4.8 mM) at 25 °C, non-thermostatted (▲ = D_{Am}, ● = D_{Eu}, ■ = $SF_{Am/Eu}$, contact time = 6 hours).

The extraction of Am(III) and Eu(III) from 4 M HNO_3 by **12** and **13** in 1-octanol as a function of time was subsequently investigated, and compared directly with the corresponding data for BTBP **1**. The dependence of the *D* value for Am(III) on contact time for 5 mM solutions of **1**, **12** and **13** in 1-octanol is shown in Figure 7. Both alkylated ligands **12** and **13** suffer from slower extraction kinetics when compared to $CyMe_4$-BTBP **1**, and equilibrium was not reached even after 30 hours of contact time. Distribution ratios for Am(III) greater than 1 are observed only after 30 hours of contact for both ligands, confirming that slow extraction kinetics is responsible for the lower *D* values for **12** and **13** compared to **1**. Alkyl substitution of $CyMe_4$-BTBP **1** at the 4- and 4'-positions of the pyridine rings thus has a deleterious effect on the rates of metal ion extraction.

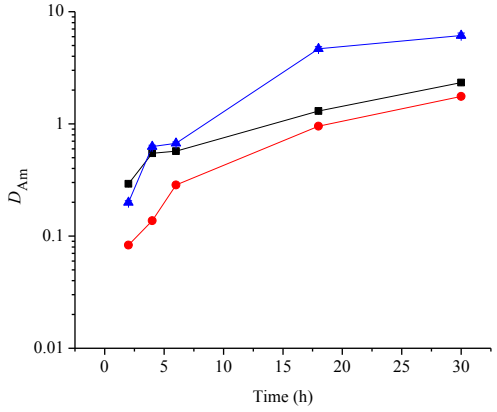


Figure 7. Extraction of Am(III) from 4 M HNO_3 as a function of contact time for BTBPs **12**, **13** and **1** in 1-octanol (5 mM for **12** and **1**, 4.8 mM for **13**) at 25 °C, non-thermostatted (■ = D_{Am} for BTBP **12**, ● = D_{Am} for BTBP **13**, ▲ = D_{Am} for BTBP **1**).

The kinetics of Am(III) and Eu(III) extraction by the BTBP ligands in 1-octanol can be improved by using a phase-transfer agent such as *N*,*N*'-dimethyl-*N*,*N*'-dioctylhexoxyethylmalonamide (DMDOHEMA)[33] or *N*,*N*,*N*',*N*'-tetraoctyldiglycolamide (TODGA).[34] Using cyclohexanone as the diluent instead of 1-octanol also increases the rates of extraction by the BTBP ligands.[35] Therefore, we next studied the extraction of Am(III) and Eu(III) by **12** and **13** (5 mmolar solutions) as a function of [HNO_3] using cyclohexanone as the diluent. The results are presented in Figures 8 and 9. The results show that the choice of diluent strongly affects the extraction properties of the ligands. For both ligands, there is a marked improvement in both the extraction efficiency and Am/Eu selectivity in cyclohexanone compared to 1-octanol. When [HNO_3] ≥ 1 M, the *D* value for Am(III) exceeds 10 and $SF_{Am/Eu}$ is close to, or exceeds 100. Although it is known that cyclohexanone participates to some extent in the non-selective extraction of both metal ions, this effect is rather small and usually negligible.[36] It is possible that a synergistic effect is taking place in the extraction by **12** and **13** in cyclohexanone that does not occur in 1-octanol. We briefly examined the extraction properties of BTBP **12** dissolved in 3-methylcyclohexanone, a diluent we have investigated recently (see Supporting Information),[36] but a detrimental effect on both the extraction ability, and the Am/Eu selectivity was observed in this diluent compared to cyclohexanone.

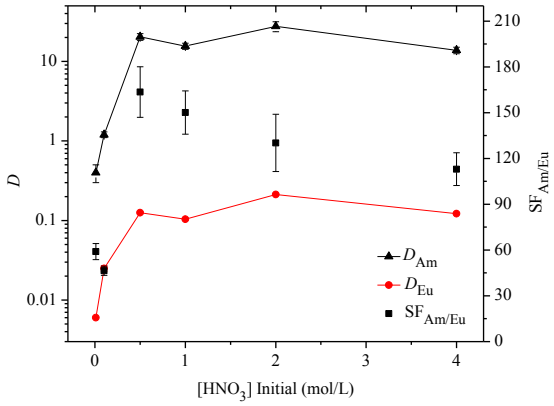


Figure 8. Extraction of Am(III) and Eu(III) as a function of [HNO_3] for BTBP **12** in cyclohexanone (5 mM) at 25 °C, non-thermostatted (▲ = D_{Am}, ● = D_{Eu}, ■ = $SF_{Am/Eu}$, contact time = 6 hours).

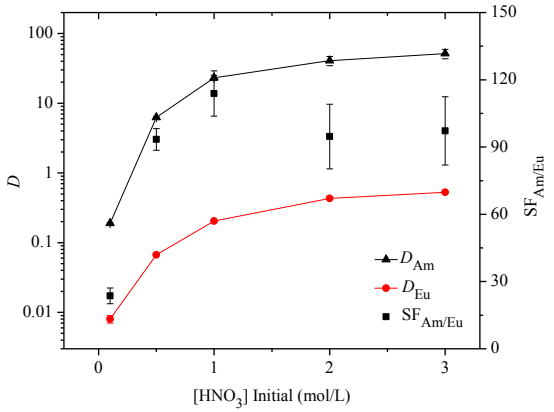


Figure 9. Extraction of Am(III) and Eu(III) as a function of [HNO_3] for BTBP **13** in cyclohexanone (5 mM) at 25 °C, non-thermostatted (▲ = D_{Am}, ● = D_{Eu}, ■ = $SF_{Am/Eu}$, contact time = 6 hours).

The variation of D_{Am} with phase contact time for both ligands **12** and **13** in cyclohexanone is shown in Figure 10. As expected, the use of cyclohexanone as the diluent leads to a considerable improvement in the kinetics of extraction compared to 1-octanol. Equilibrium is reached within 30 minutes for BTBP **12** and within 2 hours for BTBP **13**. For BTBP **12**, these extraction kinetics are comparable to other BTBP ligands investigated by us

previously,[36] but for the more lipophilic BTBP **13**, the extraction kinetics are still significantly slower than those of other BTBP ligands dissolved in cyclohexanone.[35] The relationship between the *D* values for Am(III) in cyclohexanone and the ligand concentration was then investigated to determine the metal:ligand stoichiometry of the extracted complexes. A plot of log(D_{Am}) v log[BTBP] gave a straight line with a slope of 1.79 (for BTBP **12**) and 2.01 (for BTBP **13**), confirming that 1:2 complexes were formed by both ligands, in agreement with previous studies on $CyMe_4$-BTBP **1**.[7]

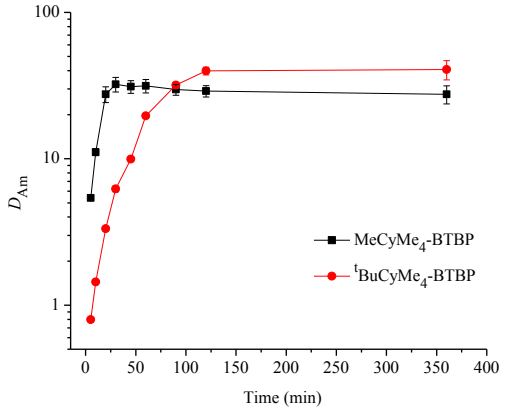


Figure 10. Extraction of Am(III) from 2 M HNO_3 as a function of contact time for BTBPs **12** and **13** in cyclohexanone (5 mM) at 25 °C, non-thermostatted (■ = D_{Am} for BTBP **12**, ● = D_{Am} for BTBP **13**).

It is known that the presence of benzylic hydrogens in the BTP and BTBP ligands leads to chemical attack at these positions by free-radical species formed during exposure of the organic and aqueous phases to the radionuclides.[37] Further studies on BTBP **12** were thus discontinued and BTBP **13** was chosen for further studies aimed at improving the kinetics of extraction into 1-octanol; the preferred diluent for process implementation. The effect of the nitric acid concentration of the aqueous phase on the distribution ratios of Am(III) and Eu(III) and on the extraction kinetics was studied to determine the optimum conditions for the extraction. The variation of the *D* values with contact time at three different concentrations of nitric acid (0.2 M, 1 M and 3 M HNO_3) show that the optimum extraction by **13** takes place from 3 M HNO_3 after 90 minutes of contact time (see Supporting Information). In the extraction from 0.2 M HNO_3, the *D* values for both metals remain below 0.1, indicating that dilute nitric acid solutions would be suitable for the back-extraction of both metals from the loaded organic phase.

The influence of the phase-transfer agents DMDOHEMA[33] and TODGA[34] on the extraction of Am(III) and Eu(III) by **13** from 3 M HNO_3 was then investigated in order to improve the slow extraction kinetics of BTBP **13**. The extraction of Am(III) and Eu(III) as a function of contact time was studied at three different concentrations of DMDOHEMA (Figure 11). Progressively higher concentrations of DMDOHEMA led to improved extractions of both metals, although equilibrium was not reached within 45 minutes of contact. The best results were observed in the presence of 0.25 M DMDOHEMA which improved the kinetics of extraction such that, after 45 minutes of contact, a D_{Am} value of 3.6 was obtained (this compares to D_{Am} = 0.959 after 45 minutes in the absence of DMDOHEMA). Similar results were observed in the presence of TODGA (D_{Am} = 3.63 after 45 minutes), although the extraction of Eu(III) was significantly higher in this case leading to a reduction in the Am/Eu separation factor (see Supporting Information).

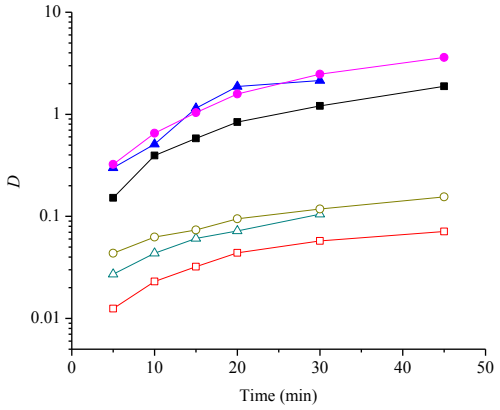


Figure 11. Extraction of Am(III) and Eu(III) from 3 M HNO_3 into 1-octanol by BTBP **13** (5 mM) as a function of contact time at different concentrations of DMDOHEMA (full symbols = D_{Am}, hollow symbols = D_{Eu}, ■/□ = *D* at 0.05 M DMDOHEMA, ▲/Δ = *D* at 0.16 M DMDOHEMA, ●/○ = *D* at 0.25 M DMDOHEMA).

Conclusions

We have reported the synthesis, lanthanide speciation and Am(III)/Eu(III) solvent extraction properties of BTBP ligands bearing additional alkyl-groups in the 4- and 4'-positions of the pyridine rings of the parent ligand $CyMe_4$-BTBP. A lower reactivity was observed in the condensation reactions of 7-membered ring α-diketones with a dicarbohydrazonamide compared to those of a 6-membered ring α-diketone. Paradoxically, the presence of the additional alkyl groups does not increase the solubilities of the ligands, and leads to extraction kinetics that are considerably slower than that found for the unsubstituted BTBPs. However, the substituted BTBPs are highly efficient and selective in the extraction and separation of Am(III) from Eu(III) both in cyclohexanone, and in 1-octanol in the presence of a phase modifier. Thus alkyl substitution of BTBP ligands does not necessarily improve their solubilities, at least in the case of symmetrical BTBPs. NMR titrations and mass spectrometry studies showed that the ligands formed both 1:1 and 1:2 complexes with La(III) and Y(III), but only 1:2 complexes with Eu(III) and Ce(III). Preliminary stability constants of the Ln(III) complexes were determined from the NMR data. The challenge of increasing the solubilities of the BTBP ligands without adversely affecting their extraction kinetics thus remains to be addressed.

Experimental Section

General Procedures: Melting points (Mp) were obtained on a Stuart SMP10 instrument and are uncorrected. IR spectra were recorded as Nujol® mulls on a Perkin Elmer RX1 FT-IR instrument. ^1H and ^{13}C-{^1H} NMR spectra were recorded using either a Bruker AMX400 or an Avance XXX400 instrument. Chemical shifts are reported in parts per million downfield from tetramethylsilane. Coupling constants (*J*) are quoted in Hertz. Assignments were verified with ^1H-^1H and ^1H-^{13}C COSY experiments as appropriate. Multiplicities and peak assignments are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (qu), multiplet (m), double doublet (dd), double triplet (dt), double quartet (dq), broad (br), apparent (app) and quaternary carbon (quat). Mass spectra were obtained under electrospray conditions on a Thermo Scientific LTQ

Orbitrap XL instrument. Elemental microanalyses were carried out by Medac Ltd., Chertsey Road, Chobham, Surrey (UK). Anhydrous diethyl ether was dried and distilled over sodium benzophenone ketyl prior to use. Diisopropylamine was dried and distilled over calcium hydride prior to use. Toluene was dried over calcium chloride prior to use. All organic reagents were obtained from either Acros or Aldrich, while inorganic reagents were obtained from either BDH or Aldrich and used as received. 3,3,6,6-Tetramethylcyclohexane-1,2-dione **11** was synthesized by a new procedure as described previously.[11,21]

Synthesis of Bis-*N*-Oxides 5 and 6. General Procedure: The 4,4'-disubstituted-2,2'-bipyridine **3** or **4** (9.00 g, 48.84 mmol for **3**, 33.53 mmol for **4**) were dissolved in acetic acid (50 mL) and hydrogen peroxide (27.66 mL for **3**, 19.00 mL for **4**, 30 %, 5 eq) was added dropwise. The solution was stirred at 100 °C for 4 h. The solution was allowed to cool to room temperature and hydrogen peroxide (27.66 mL for **3**, 19.00 mL for **4**, 30 %, 5 eq) was added dropwise. The solution was stirred at 100 °C for 4 h. The solution was allowed to cool to room temperature and stirring was continued for a further 24 h. Solid sodium hydrogen carbonate was added until the solution became basic and the solution was extracted with chloroform (3 × 100 mL). The combined organic phases were dried over sodium sulfate and evaporated to afford the product **5** or **6**.

4,4'-Dimethyl-2,2'-bipyridine 1,1'-dioxide 5:[16,17] Yellow solid (7.89 g, 74 %). ^{1}H NMR (400.1 MHz, $CDCl_3$, Me_4Si): δ = 8.27 (2H, d, *J* = 6.6 Hz, 6-Ar*H* and 6'-Ar*H*), 7.51 (2H, app s, 3-Ar*H* and 3'-Ar*H*), 7.17 (2H, app d, *J* = 6.6 Hz, 5-Ar*H* and 5'-Ar*H*), 2.39 (6H, s, 4-CH_3 and 4'-CH_3) ppm. HRMS (CI): *m/z* = 217.0965 [M + H$^+$]; $C_{12}H_{13}N_2O_2$ requires 217.0977.

4,4'-Di-*tert*-butyl-2,2'-bipyridine 1,1'-dioxide 6:[17,18] Yellow foamy solid (9.72 g, 96 %). ^{1}H NMR (400.1 MHz, $CDCl_3$, Me_4Si): δ = 8.25 (2H, d, *J* = 8.0 Hz, 6-Ar*H* and 6'-Ar*H*), 7.64 (2H, d, *J* = 4.0 Hz, 3-Ar*H* and 3'-Ar*H*), 7.33 (2H, dd, *J* = 8.0 and 4.0 Hz, 5-Ar*H* and 5'-Ar*H*), 1.35 (18H, s, 4-C(CH_3)$_3$ and 4'-C(CH_3)$_3$) ppm. HRMS (CI): *m/z* = 301.1918 [M + H$^+$]; $C_{18}H_{25}N_2O_2$ requires 301.1916.

Synthesis of Dicarbonitriles 7 and 8. General Procedure: The bis-*N*-oxide **5** or **6** (7.89 g, 36.52 mmol for **5**, 13.53 g, 45.10 mmol for **6**) was suspended in DCM (130 mL for **5**, 200 mL for **6**) and trimethylsilyl cyanide (15.99 mL, 127.84 mmol for **5**, 19.74 mL, 157.85 mmol for **6**, 3.5 eq) was added. Benzoyl chloride (14.84 mL, 127.84 mmol for **5**, 18.32 mL, 157.85 mmol for **6**, 3.5 eq) was slowly added over 15 minutes and the solution was stirred at room temperature for 24 h and then heated under reflux for 2 days. The solution was allowed to cool to room temperature and DCM (100 mL) was added. The undissolved solid was filtered and washed with solvents (MeOH (15 mL) and ether (15 mL) for **5**, DCM (20 mL) for **6**) and allowed to dry in air to afford the product **7** or **8** (0.49 g for **7**, 8.11 g for **8**). 10 % Potassium carbonate solution (150 mL) was added to the filtrate and the phases were vigorously stirred for 15 min. The phases were separated and the aqueous phase was extracted with DCM (25 mL). The combined organic phases were dried ($MgSO_4$) and evaporated to yield a semi-solid which was triturated with MeOH (100 mL) and filtered and washed with MeOH (100 mL) and ether (50 mL) to yield the product **7** or **8** (3.83 g for **7**, 1.97 g for **8**).

4,4'-Dimethyl-2,2'-bipyridine-6,6'-dicarbonitrile 7:[17,19] Off-white solid. Total yield: 4.32 g (50 %). ^{1}H NMR (400.1 MHz, $CDCl_3$, Me_4Si): δ = 8.52 (2H, app q, *J* = 0.7 Hz, 3-Ar*H* and 3'-Ar*H*), 7.58 (2H, app q, *J* = 0.7 Hz, 5-Ar*H* and 5'-Ar*H*), 2.54 (6H, s, 4-CH_3 and 4'-CH_3) ppm. HRMS (CI): *m/z* = 235.0979 [M + H$^+$]; $C_{14}H_{11}N_4$ requires 235.0984.

4,4'-Di-*tert*-butyl-2,2'-bipyridine-6,6'-dicarbonitrile 8:[17] White solid. Total yield: 10.08 g (70 %). ^{1}H NMR (400.1 MHz, $CDCl_3$, Me_4Si): δ = 8.68 (2H, d, *J* = 1.9 Hz, 3-Ar*H* and 3'-Ar*H*), 7.75 (2H, d, *J* = 1.9 Hz, 5-Ar*H* and 5'-Ar*H*), 1.42 (18H, s, 4-C(CH_3)$_3$ and 4'-C(CH_3)$_3$) ppm. HRMS (CI): *m/z* = 319.1926 [M + H$^+$]; $C_{20}H_{23}N_4$ requires 319.1923.

Synthesis of Dicarbohydrazonamides 9 and 10. General Procedure: To a suspension of the dicarbonitrile **7** or **8** (1.08 g, 4.61 mmol for **7**, 10.08 g, 31.69 mmol for **8**) in EtOH (80 mL for **7**, 300 mL for **8**) was added hydrazine hydrate (30 mL, 64 % for **7**, 150 mL, 64 % for **8**). The suspension was stirred at room temperature for 14 days. In the case of **8**, the suspension was stirred at 60–70 °C for an additional 2 days giving a clear solution. Water (400 mL for **7**, 3 L for **8**) was added and the precipitated solid was filtered and washed with water (150 mL for **7**, 400 mL for **8**) and allowed to dry in air overnight to afford the product **9** or **10**.

4,4'-Dimethyl-2,2'-bipyridine-6,6'-dicarbohydrazonamide 9: White solid (1.12 g, 81 %). Mp above 300 °C (from H_2O/EtOH). $C_{14}H_{18}N_8$ (298.16): calcd. C 56.36, H 6.08, N 37.54 %; found C 55.97, H 5.74, N 37.42 %. IR ν_{max} (Nujol): 3439 (NH_2), 3346 (NH_2), 2917, 1626, 1591, 1454, 1374, 1231, 1160, 1026, 990, 869, 828, 779, 754 cm^{-1}. ^{1}H NMR (400.1 MHz, DMSO-d_6): δ = 8.44 (2H, app q, *J* = 0.7 Hz, 3-Ar*H* and 3'-Ar*H*), 7.79 (2H, app q, *J* = 0.7 Hz, 5-Ar*H* and 5'-Ar*H*), 5.96 (4H, br s, 2 × NH_2), 5.48 (4H, br s, 2 × NH_2), 2.44 (6H, s, 4-CH_3 and 4'-CH_3) ppm. ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 153.1 (2 × quat), 151.1 (2 × quat), 147.7 (2 × quat), 120.9 (C-3 and C-3'), 119.7 (C-5 and C-5'), 113.6 (2 × H_2NC=NNH$_2$), 20.8 (4-*C*H$_3$ and 4'-*C*H$_3$) ppm. HRMS (CI): *m/z* = 299.1725 [M + H$^+$]; $C_{14}H_{19}N_8$ requires 299.1727.

4,4'-Di-*tert*-butyl-2,2'-bipyridine-6,6'-dicarbohydrazonamide 10: Light brown solid (9.63 g, 79 %). Mp above 300 °C (from H_2O/EtOH). $C_{20}H_{30}N_8$ (382.25): calcd. C 62.80, H 7.90, N 29.28 %; found C 62.46, H 7.51, N 28.83 %. IR ν_{max} (Nujol): 3438 (NH_2), 3325 (NH_2), 2916, 1647, 1585, 1545, 1456, 1376, 1268, 1201, 1144, 1031, 994, 884, 725 cm^{-1}. ^{1}H NMR (400.1 MHz, DMSO-d_6): δ = 8.45 (2H, d, *J* = 1.8 Hz, 3-Ar*H* and 3'-Ar*H*), 7.99 (2H, d, *J* = 1.8 Hz, 5-Ar*H* and 5'-Ar*H*), 5.88 (4H, br s, 2 × NH_2), 5.38 (4H, br s, 2 × NH_2), 1.37 (18H, s, 4-C(CH_3)$_3$ and 4'-C(CH_3)$_3$) ppm. ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 160.4 (2 × quat), 153.6 (2 × quat), 151.4 (2 × H_2NC=NNH$_2$), 143.4 (2 × quat), 117.2 (C-3 and C-3'), 115.7 (C-5 and C-5'), 34.8 (4-*C*(CH$_3$)$_3$ and 4'-*C*(CH$_3$)$_3$), 30.2 (4-C(*C*H$_3$)$_3$ and 4'-C(*C*H$_3$)$_3$) ppm. HRMS (CI): *m/z* = 383.2670 [M + H$^+$]; $C_{20}H_{31}N_8$ requires 383.2666.

Synthesis of BTBP Ligands 12 and 13. General Procedure: The dicarbohydrazonamide **9** or **10** (0.50 g, 1.67 mmol for **9**, 2.00 g, 5.23 mmol for **10**) was suspended in dioxane (50 mL for **9**, 150 mL for **10**) and 3,3,6,6-tetramethylcyclohexane-1,2-dione **11** (0.62 g, 3.69 mmol for **9**, 1.93 g, 11.51 mmol for **10**, 2.2 eq) was added. Triethylamine (5 mL for **9**, 15 mL for **10**) was added and the suspension was heated under reflux for 3 days. The suspension was allowed to cool to room temperature and the insoluble solid was filtered and washed with DCM (10 mL). The filtrate was evaporated under reduced pressure to afford a yellow solid which was triturated with MeOH (50 mL). The insoluble solid was filtered and washed with MeOH (80 mL) and diethyl ether (40 mL) to afford the pure ligand **12** or **13**.

4,4'-Dimethyl-6,6'-bis(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-1,2,4-benzotriazin-3-yl)-2,2'-bipyridine 12: Yellow solid (0.46 g, 49 %). Mp 286 °C (from MeOH). $C_{34}H_{42}N_8$ (562.35): calcd. C 72.57, H 7.52, N 19.90 %; found C 72.14, H 7.80, N 19.65 %. IR ν_{max} (Nujol): 2916, 1588, 1556, 1507, 1456, 1376, 1349, 1249, 1142, 1048, 1015, 929, 867, 832, 717, 682 cm^{-1}. ^{1}H NMR (400.1 MHz, $CDCl_3$, Me_4Si): δ = 8.78 (2H, app q, *J* = 0.7 Hz, 3-Ar*H* and 3'-Ar*H*), 8.32 (2H, app q, *J* = 0.7 Hz, 5-Ar*H* and 5'-Ar*H*), 2.58 (6H, s, 4-CH_3 and 4'-CH_3), 1.89 (8H, s, 4 × CH_2), 1.53 (12H, s, 4 × CH_3), 1.47 (12H, s, 4 × CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, Me_4Si): δ = 164.2 (2 × quat), 162.9 (2 × quat), 161.0 (2 × quat), 156.0 (2 × quat), 152.6 (2 × quat), 149.1 (2 × quat), 124.8 (C-5 and C-5'), 123.7 (C-3 and C-3'), 37.2 (2 × quat), 36.4 (2 × quat), 33.8 (2 × *C*H$_2$), 33.3 (2 × *C*H$_2$), 29.7 (4 × *C*H$_3$), 29.2 (4 × *C*H$_3$), 21.5 (4-*C*H$_3$ and 4'-*C*H$_3$) ppm. HRMS (CI): *m/z* = 563.3606 [M + H$^+$]; $C_{34}H_{43}N_8$ requires 563.3605.

4,4'-Di-*tert*-butyl-6,6'-bis(5,5,8,8-tetramethyl-5,6,7,8-tetrahydro-1,2,4-benzotriazin-3-yl)-2,2'-bipyridine 13: Yellow solid (0.71 g, 21 %). Mp above 300 °C (from MeOH). $C_{40}H_{54}N_8$ (646.44): calcd. C 74.27, H 8.41, N 17.31 %; found C 73.92, H 8.43, N 17.01 %. IR ν_{max} (Nujol): 2921, 1591, 1550, 1510, 1456, 1376, 1346, 1260, 1161, 1099, 1061, 894, 854, 720 cm^{-1}. ^1H NMR (400.1 MHz, $CDCl_3$, Me_4Si): δ = 8.96 (2H, d, *J* = 1.8 Hz, 3-Ar*H* and 3'-Ar*H*), 8.65 (2H, d, *J* = 1.8 Hz, 5-Ar*H* and 5'-Ar*H*), 1.91 (8H, s, 4 × CH_2), 1.53 (12H, s, 4 × CH_3), 1.51 (12H, s, 4 × CH_3), 1.48 (18H, s, 4-C(CH_3)$_3$ and 4'-C(CH_3)$_3$) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, Me_4Si): δ = 164.7 (2 × quat), 162.7 (2 × quat), 162.0 (2 × quat), 161.6 (2 × quat), 156.4 (2 × quat), 152.6 (2 × quat), 121.1 (C-5 and C-5'), 119.6 (C-3 and C-3'), 37.3 (2 × quat), 36.4 (2 × quat), 35.3 (4-*C*(CH$_3$)$_3$ and 4'-*C*(CH$_3$)$_3$), 33.8 (2 × *C*H$_2$), 33.3 (2 × *C*H$_2$), 30.6 (4-C(*C*H$_3$)$_3$ and 4'-C(*C*H$_3$)$_3$), 29.8 (4 × *C*H$_3$), 29.1 (4 × *C*H$_3$) ppm. HRMS (CI): *m*/*z* = 647.4529 [M + H$^+$]; $C_{40}H_{55}N_8$ requires 647.4544.

Diethyl 2,2,6,6-tetramethylheptanedioate 15:[23b] Anhydrous diethyl ether (240 mL) was placed in an oven-dried 500 mL 3-neck flask and sealed under an atmosphere of nitrogen. Diisopropylamine (34.6 mL, 246.87 mmol, 1.1 eq) was added via syringe and the solution was cooled to −20 °C. *n*-Butyllithium (89.7 mL, 2.5 M, 224.43 mmol, 1 eq) was added dropwise via syringe and the solution was stirred at −20 °C for 15 min. Ethyl isobutyrate **14** (30.0 mL, 26.07 g, 224.43 mmol) was added dropwise via syringe over 30 min and the solution was allowed to warm to room temperature and stirred for an additional 1 h. 1,3-Diiodopropane (12.88 mL, 112.21 mmol, 0.5 eq) was added dropwise over 15 min and the solution was heated under reflux for 24 h. The flask was allowed to cool to room temperature, the solution was quenched with satd. aq. ammonium chloride (150 mL) and the phases were mixed and separated. The aqueous phase was extracted with diethyl ether (2 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to afford a yellow liquid (42.95 g) which was purified by vacuum distillation using a Vigreux column to afford the product **15** as a colourless liquid (17.35 g, 56 %). Bp = 86–92 °C at 0.1 mm Hg. ^1H NMR (400.1 MHz, $CDCl_3$, Me_4Si): δ = 4.10 (4H, q, *J* = 7.8 Hz, 2 × $CO_2CH_2CH_3$), 1.46–1.50 (4H, m, 3-CH_2 and 5-CH_2), 1.23 (6H, t, *J* = 7.8 Hz, 2 × $CO_2CH_2CH_3$), 1.17 (2H, s, 4-CH_2), 1.14 (12H, s, 2 × 2-CH_3 and 2 × 6-CH_3) ppm.

3,3'-Thiobis(2,2-dimethylpropanoic acid) 19:[26a,26b,27,38] Chloropivalic acid **18** (50.37 g, 368.79 mmol) was suspended in water (45 mL) and solid sodium carbonate (19.54 g, 184.39 mmol, 0.5 eq) was added. A solution of sodium sulfide nonahydrate (44.28 g, 184.39 mmol, 0.5 eq) in water (35 mL) was added dropwise over 10 min. The solution was stirred at 45–50 °C for 24 h. The flask was cooled to room temperature and 50 % aqueous sulfuric acid (ca. 100 mL) was added in small aliquots with stirring. The precipitated solid was filtered and washed with water (50 mL) and allowed to dry in air. The solid was dried at 70 °C for 2 days to afford the product **19** as a pale brown solid (28.90 g, 66 %). ^1H NMR (400.1 MHz, MeOD): δ = 2.82 (4H, s, 3-CH_2 and 3'-CH_2), 1.24 (12H, s, 2 × 2-CH_3 and 2 × 2'-CH_3) ppm.

Diethyl 3,3'-thiobis(2,2-dimethylpropanoate) 20:[23b,26a,26b,27,38] The diacid **19** (34.62 g, 147.94 mmol) was dissolved in EtOH (150 mL) and benzene (100 mL) and conc. sulfuric acid (5 mL) was added. The solution was heated under reflux for 24 h. The flask was allowed to cool to room temperature and the solution was diluted with diethyl ether (100 mL). The solution was washed with water (2 × 75 mL), dilute aqueous sodium hydrogen carbonate (2 × 50 mL), dried ($MgSO_4$) and evaporated to yield a brown liquid (36.85 g) which was purified by vacuum distillation using a Vigreux column to afford the product **20** as a colourless liquid (32.33 g, 75 %). Bp = 108–110 °C at 0.1 mm Hg. ^1H NMR (400.1 MHz, $CDCl_3$, Me_4Si): δ = 4.14 (4H, q, *J* = 8.0 Hz, 2 × $CO_2CH_2CH_3$), 2.77 (4H, s, 3-CH_2 and 3'-CH_2), 1.26 (6H, t, *J* = 8.0 Hz, 2 × $CO_2CH_2CH_3$), 1.23 (12H, s, 2 × 2-CH_3 and 2 × 2'-CH_3) ppm.

Intramolecular Acyloin Reactions of Diesters 15 and 20. General Procedure: Dry toluene (300 mL) was placed in an oven-dried flask and sealed under nitrogen. Freshly cut sodium (10.99 g, 478.12 mmol for **15**, 12.82 g, 557.41 mmol for **20**, 5 eq) was added and the flask was heated under reflux until the sodium melted. The diester **15** or **20** (26.01 g, 95.62 mmol for **15**, 32.33 g, 111.48 mmol for **20**) was added and then chlorotrimethylsilane (60.44 mL, 478.12 mmol for **15**, 70.47 mL, 557.41 mmol for **20**, 5 eq) was added. The mixture was heated under reflux for 24 h. The mixture was allowed to cool to room temperature and was filtered through a sintered disk under nitrogen using a wide Schlenk tube. The solid residue was washed with toluene (100 mL) and THF (50 mL) and the filtrate was evaporated under reduced pressure to afford a liquid which was purified by vacuum distillation using a Vigreux column to afford the product **16** or **21**. The excess sodium was quenched under nitrogen by washing the solid residue with EtOH (150 mL).

1,2-Bis(trimethylsilyloxy)-3,3,7,7-tetramethylcyclohept-1-ene 16:[23] Colourless liquid (12.88 g, 41 %). Bp = 72–80 °C at 0.1 mm Hg. ^1H NMR (400.1 MHz, $CDCl_3$, Me_4Si): δ = 1.41–1.48 (6H, m, 4-CH_2, 5-CH_2 and 6-CH_2), 0.92 (12H, s, 2 × 3-CH_3 and 2 × 7-CH_3), 0.00 (18H, s, 2 × OSi(CH_3)$_3$) ppm.

4,5-Bis(trimethylsilyloxy)-3,3,6,6-tetramethyl-2,3,6,7-tetrahydrothiepine 21:[23] Colourless liquid (22.12 g, 57 %). Bp = 104–108 °C at 0.1 mm Hg. ^1H NMR (400.1 MHz, $CDCl_3$, Me_4Si): δ = 2.44 (4H, br s, 2-CH_2 and 7-CH_2), 1.07 (12H, s, 2 × 3-CH_3 and 2 × 6-CH_3), 0.00 (18H, s, 2 × OSi(CH_3)$_3$) ppm.

Synthesis of α-Diketones 17 and 22. General Procedure:[39] The starting material **16** or **21** (12.88 g, 39.26 mmol for **16**, 22.12 g, 63.93 mmol for **21**) was dissolved in carbon tetrachloride (130 mL) and bromine (2.01 mL, 39.26 mmol for **16**, 3.27 mL, 63.93 mmol for **21**, 1 eq) was added dropwise over 15 min. The solution was stirred at room temperature for 30 min. The solution was then washed with water (2 × 50 mL) and satd. aq. sodium sulfite (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to yield a liquid which was purified by vacuum distillation using a Vigreux column to afford the product diketone **17** or **22**.

3,3,7,7-Tetramethylcycloheptane-1,2-dione 17:[23–25] Pale brown liquid (5.34 g, 74 %). Bp = 158–160 °C at 10–20 mm Hg. ^1H NMR (400.1 MHz, $CDCl_3$, Me_4Si): δ = 1.71–1.77 (2H, m, 5-CH_2), 1.64–1.68 (4H, m, 4-CH_2 and 6-CH_2), 1.15 (12H, s, 2 × 3-CH_3 and 2 × 7-CH_3) ppm.

3,3,6,6-Tetramethylthiepane-4,5-dione 22:[23,24,26] Yellow liquid (12.06 g, 94 %). Bp = 82–84 °C at 0.1 mm Hg. ^1H NMR (400.1 MHz, $CDCl_3$, Me_4Si): δ = 2.59 (4H, s, 2-CH_2 and 7-CH_2), 1.27 (12H, s, 2 × 3-CH_3 and 2 × 6-CH_3) ppm.

Synthesis of Crude BTBP Ligands 24 and 25. General Procedure: The dicarbohydrazonamide **23** (0.10 g, 0.37 mmol) was suspended in pyridine (20 mL) and diketone **17** or **22** (0.15 g for **17**, 0.16 g for **22**, 0.81 mmol, 2.2 eq) was added. The suspension was heated under reflux for 3 days. The suspension was allowed to cool to room temperature and the insoluble solid was filtered and washed with pyridine (10 mL). The filtrate was evaporated under reduced pressure to afford the crude ligand **24** or **25** as a yellow semi-solid. Attempted purification by trituration with MeOH and ether, recrystallization from DCM/hexane or chromatography on silica (2.5 % MeOH in DCM) was unsuccessful and pure samples of **24** and **25** could not be obtained.

6,6'-Bis(5,5,9,9-tetramethyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[*e*]1,2,4-triazin-3-yl)-2,2'-bipyridine 24: The ligand had ^1H NMR (400.1 MHz, $CDCl_3$, Me_4Si): δ = 8.96 (2H, dd, *J* = 7.8 and 0.9 Hz, 3-Ar*H* and 3'-Ar*H*), 8.56 (2H, dd, *J* = 7.8 and 0.9 Hz, 5-Ar*H* and 5'-Ar*H*), 8.05 (2H, t, *J* = 7.8 Hz, 4-Ar*H* and 4'-Ar*H*), 1.97–2.02 (4H, m, 2 × 7-CH_2), 1.86–1.91 (8H, m,

2 × 6-CH_2 and 2 × 8-CH_2), 1.56 (12H, s, 4 × CH_3), 1.52 (12H, s, 4 × CH_3) ppm.

6,6'-Bis(5,5,9,9-tetramethyl-5,6,8,9-tetrahydrothiepino[4,5-*e*]-1,2,4-triazin-3-yl)-2,2'-bipyridine 25: The ligand had ^{1}H NMR (400.1 MHz, $CDCl_3$, Me_4Si): δ = 8.95 (2H, dd, *J* = 7.8 and 0.8 Hz, 3-Ar*H* and 3'-Ar*H*), 8.56 (2H, dd, *J* = 7.8 and 0.8 Hz, 5-Ar*H* and 5'-Ar*H*), 8.08 (2H, t, *J* = 7.8 Hz, 4-Ar*H* and 4'-Ar*H*), 2.90 (4H, s, 2 × 6-CH_2), 2.89 (4H, s, 2 × 8-CH_2), 1.67 (12H, s, 4 × CH_3), 1.64 (12H, s, 4 × CH_3) ppm.

Synthesis of Pd(II) Complex of BTBP Ligand 13: Ligand **13** (0.10 g, 0.154 mmol) was dissolved in MeOH (20 mL) and $Pd(OAc)_2$ (0.034 g, 0.154 mmol, 1 eq) was added. The solution was heated under reflux for 3 h. The solution was allowed to cool to room temperature and a saturated solution of ammonium hexafluorophosphate in MeOH (10 mL) was added. The solution was evaporated and the solid was triturated with water (50 mL) and then filtered, washed with water (50 mL) and allowed to dry in air to afford the complex as a brown solid (0.13 g, 81 %). Mp 261–262 ºC (decomposition). $C_{40}H_{54}N_8P_2F_{12}Pd$ (1042.27): calcd. C 46.05, H 5.22, N 10.74, F 21.85, Pd 10.20 %; found C 45.78, H 4.83, N 10.44, F 21.67, Pd 10.28 %. IR ν_{max} (Nujol): 2967, 2873, 1611, 1538, 1475, 1459, 1376, 1366, 1264, 1242, 1153, 1118, 1092, 1048, 1025, 935, 896, 835, 827, 627, 556 cm^{-1}. ^{1}H NMR (400.1 MHz, acetone-d_6): δ = 8.99 (2H, app s, 3-C*H* and 3'-C*H*), 8.70 (2H, app s, 5-C*H* and 5'-C*H*), 2.04 (8H, s, 4 × CH_2), 1.61 (12H, s, 4 × CH_3), 1.56 (30H, s, 4 × CH_3, 4-C(CH_3)$_3$ and 4'-C(CH_3)$_3$) ppm. ^{13}C NMR (100.6 MHz, acetone-d_6): δ = 173.4 (2 × quat), 172.7 (2 × quat), 167.5 (2 × quat), 167.0 (2 × quat), 158.0 (2 × quat), 152.6 (2 × quat), 126.8 (3-*C*H and 3'-*C*H), 125.2 (5-*C*H and 5'-*C*H), 39.6 (2 × quat), 38.4 (2 × quat), 38.2 (4-*C*(CH$_3$)$_3$ and 4'-*C*(CH$_3$)$_3$), 33.3 (2 × *C*H$_2$), 33.0 (2 × *C*H$_2$), 30.3 (4-C(*C*H$_3$)$_3$ and 4'-C(*C*H$_3$)$_3$), 29.7 (4 × *C*H$_3$), 29.2 (4 × *C*H$_3$) ppm.

Solvent Extraction Experiments: The aqueous solutions were prepared by spiking nitric acid solutions (0.01–4 mol dm^{-3}) with stock solutions of ^{241}Am and ^{152}Eu tracers in nitric acid. The stock solution of ^{241}Am in 0.5 M HNO_3 was prepared by dissolving americium oxide in 5 M HNO_3 and subsequent dilution with water. The stock solution of ^{152}Eu was prepared by appropriate dilution of a commercial preparation (REu-2) supplied by Polatom (Poland). Solutions of the ligands **12** and **13** (0.0048–0.005 mol dm^{-3}) were prepared by dissolving in the appropriate diluent with or without an additional phase modifier. Prior to labelling, the aqueous phases were pre-equilibrated with the neat diluents by shaking them for 4 h at 400 min^{-1} and volume ratio of 4:1. The organic phases were pre-equilibrated with the respective non-labelled aqueous phases by shaking them for 4 h at 400 min^{-1} and volume ratio of 1:1. In each case, 1.2 mL of labelled aqueous phases were prepared from which 200 µL standards were taken (to allow for mass balance calculations) prior to contacting the aqueous phases with the organic phases. Each organic phase (1 mL) was shaken separately with each of the aqueous phases for 6 h at ambient temperature (ca. 25 ºC, non-thermostatted) using an GFL 3005 Orbital Shaker (250 min^{-1}). After phase separation by centrifugation, two parallel 200 µL aliquots of each phase were withdrawn for analysis. The same procedure was used to investigate the kinetics of ^{241}Am extraction. Activity measurements of ^{241}Am and ^{152}Eu were performed with a γ-ray spectrometer EG&G Ortec (USA) with a PGT (USA) HPGe detector. The γ-lines at 59.5 keV, and 121.8 keV were examined for ^{241}Am, and ^{152}Eu, respectively. The errors given in the figures are 1σ and are based on counting statistics, only. The approximate solubilities of **12** and **13** were determined by stepwise dissolution of a known mass of the ligand in the appropriate solvent. The solvent was then added incrementally in 200 µL aliquots followed by ultrasound after each addition until a clear solution was obtained. The resulting solutions were used in the solvent extraction tests.

NMR Titrations and Stability Constant Determination: Stock solutions (0.01 M) of the ligand **13** and of the metal nitrate salts $La(NO_3)_3.6H_2O$, $Eu(NO_3)_3.5H_2O$, $Ce(NO_3)_3.6H_2O$ and $Y(NO_3)_3.6H_2O$ (Aldrich) were prepared in the appropriate deuterated solvent ($CDCl_3$ for **13**, CD_3CN for the metal salts). For solubility reasons, $CDCl_3$ was used to dissolve the ligand **13**, rather than CD_3CN. A 0.5 mL aliquot of the ligand solution was placed in an NMR tube and the ^{1}H NMR spectrum was recorded. The appropriate lanthanide salt solution was added to the NMR tube in 50 µL aliquots (ie: 0.1 equivalents each time) using a calibrated Eppendorf 100 µL micropipette, the tube was inverted several times to ensure full mixing and the ^{1}H NMR spectrum was recorded after each successive addition until the resonances of the free ligand had completely dissappeared and/or until no further spectral changes were observed. Homogeneous solutions were obtained after each addition. The relative ratios of the different species present were calculated from the relative integrals of a suitable one-proton resonance of **13**. These values were normalized such that, for a given one-proton resonance, the total integration for all species present equals one. The species distribution at different metal:ligand ratios was calculated from these normalized relative ratios. The model used for the description of a given complexation reaction consists of two balanced equations (one for ligand **13** and the second one for the metal) and equations for two or three equilibrium constants (stability constants). The Newton-Raphson[40] multidimensional non-linear regression procedure was used to solve this set of equations to determine the values of the stability constants. In the course of regression, the experimentally determined data are fitted (compared) with the calculated data and, lastly, the so called goodness-of-fit is evaluated by the χ^2-test. The value of χ^2 is used for calculating the WSOS/DF criterion (weighted sum of squares – ie: squares of deviations of the experimental values from the calculated values, divided by degrees of freedom).[41] A value of WSOS/DF ≤ 20 indicates a good agreement between the experimental and calculated data. The code used for the calculation, PMeBTBP1.fm (Code Package STAMB-2011), was constructed using the software product FAMULUS.[42] See the Supporting Information for further details.

Supporting Information (see footnote on the first page of this article):. NMR stack plots, ESI-MS peaks and species distribution graphs for lanthanide complexes of ligand **13**. Details of stability constant determination. Tables and graphs of solvent extraction data.

Acknowledgments

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[1] a) J. N. Mathur, M. S. Murali, K. L. Nash, *Solvent Extr. Ion Exch.* **2001**, *19*, 357–390; b) C. Madic, M. J. Hudson, J.-O. Liljenzin, J.-P. Glatz, R. Nannicini, A. Facchini, Z. Kolarik, R. Odoj, *Progr. Nucl. Energ.* **2002**, *40*, 523–526; c) M. J. Hudson, *Czech. J. Phys.* **2003**, *53*, A305–A311; d) C. Madic, B. Boullis, P. Baron, F. Testard, M. J. Hudson, J.-O. Liljenzin, B. Christiansen, M. Ferrando, A. Facchini, A. Geist, G. Modolo, A. G. Espartero, J. De Mendoza, *J. Alloys Compd.* **2007**, *444–445*, 23–27.

[2] J. Magill, V. Berthou, D. Haas, J. Galy, R. Schenkel, H.-W. Wiese, G. Heusener, J. Tommasi, G. Youinou, *Nuclear Energy* **2003**, *42*, 263–277.

[3] M. Salvatores, G. Palmiotti, *Progress in Particle and Nuclear Physics* **2011**, *66*, 144–166.

[4] a) H. H. Dam, D. N. Reinhoudt, W. Verboom, *Chem. Soc. Rev.* **2007**, *36*, 367–377; b) C. Ekberg, A. Fermvik, T. Retegan, G. Skarnemark, M. R. S. Foreman, M. J. Hudson, S. Englund, M. Nilsson, *Radiochim. Acta* **2008**, *96*, 225–233; c) Z. Kolarik, *Chem. Rev.* **2008**, *108*, 4208–4252; d) B. J. Mincher, G. Modolo, S. P. Mezyk, *Solvent Extr. Ion Exch.* **2010**, *28*, 415–436; e) F. W. Lewis, M. J. Hudson, L. M. Harwood, *Synlett* **2011**, 2609–2632.

[5] See for example: a) M. G. B. Drew, D. Guillaneux, M. J. Hudson, P. B. Iveson, C. Madic, *Inorg. Chem. Commun.* **2001**, *4*, 462–466; b) C. Boucher, M. G. B. Drew, P. Giddings, L. M. Harwood, M. J. Hudson, P. B. Iveson, C. Madic, *Inorg. Chem. Commun.* **2002**, *5*, 596–599; c) S. Colette, B. Amekraz, C. Madic, L. Berthon, G. Cote, C. Moulin, *Inorg. Chem.* **2002**, *41*, 7031–7041 ; d) S. Colette, B. Amekraz, C. Madic, L. Berthon, G. Cote, C. Moulin, *Inorg. Chem.* **2003**, *42*, 2215–2226; e) S. Colette, B. Amekraz, C. Madic, L. Berthon, G. Cote, C. Moulin, *Inorg. Chem.* **2004**, *43*, 6745–6751; f) M. A. Denecke, A. Rossberg, P. J. Panak, M. Weigl, B. Schimmelpfennig, A. Geist, *Inorg. Chem.* **2005**, *44*, 8418–8425; g) M. G. B. Drew, M. R. St. J. Foreman, A. Geist, M. J. Hudson, F. Marken, V. Norman, M. Weigl, *Polyhedron* **2006**, *25*, 888–900; h) N. L. Banik, B. Schimmelpfennig, C. M. Marquardt, B. Brendebach, A. Geist, M. A. Denecke, *Dalton Trans.* **2010**, *39*, 5117–5122.

[6] See for example: a) M. G. B. Drew, M. R. S. J. Foreman, C. Hill, M. J. Hudson, C. Madic, *Inorg. Chem. Commun.* **2005**, *8*, 239–241; b) J.-C. Berthet, P. Thuéry, J.-P. Dognon, D. Guillaneux, M. Ephritikhine, *Inorg. Chem.* **2008**, *47*, 6850–6862; c) J.-C. Berthet, P. Thuéry, M. R. S. Foreman, M. Ephritikhine, *Radiochim. Acta* **2008**, *96*, 189–197; d) J.-C. Berthet, G. Siffredi, P. Thuéry, M. Ephritikhine, *Dalton Trans.* **2009**, 3478–3494; e) S. Trumm, G. Lieser, M. R. S. J. Foreman, P. J. Panak, A. Geist, T. Fanghänel, *Dalton Trans.* **2010**, *39*, 923–929; f) V. Hubscher-Bruder, J. Haddaoui, S. Bouhroum, F. Arnaud-Neu, *Inorg. Chem.* **2010**, *49*, 1363–1371; g) J.-C. Berthet, J. Maynadié, P. Thuéry, M. Ephritikhine, *Dalton Trans.* **2010**, *39*, 6801–6807.

[7] A. Geist, C. Hill, G. Modolo, M. R. St. J. Foreman, M. Weigl, K. Gompper, M. J. Hudson, C. Madic, *Solvent Extr. Ion Exch.* **2006**, *24*, 463–483.

[8] M. R. S. Foreman, M. J. Hudson, M. G. B. Drew, C. Hill, C. Madic, *Dalton Trans.* **2006**, 1645–1653.

[9] D. Magnusson, B. Christiansen, M. R. S. Foreman, A. Geist, J.-P. Glatz, R. Malmbeck, G. Modolo, D. Serrano-Purroy, C. Sorel, *Solvent Extr. Ion Exch.* **2009**, *27*, 97–106.

[10] M. J. Hudson, C. E. Boucher, D. Braekers, J. F. Desreux, M. G. B. Drew, M. R. St J. Foreman, L. M. Harwood, C. Hill, C. Madic, F. Marken, T. G. A. Youngs, *New J. Chem.* **2006**, *30*, 1171–1183.

[11] F. W. Lewis, L. M. Harwood, M. J. Hudson, M. G. B. Drew, J. F. Desreux, G. Vidick, N. Bouslimani, G. Modolo, A. Wilden, M. Sypula, T.-H. Vu, J.-P. Simonin, *J. Am. Chem. Soc.* **2011**, *133*, 13093–13102.

[12] A. Fermvik, C. Ekberg, S. Englund, M. R. S. J. Foreman, G. Modolo, T. Retegan, G. Skarnemark, *Radiochim. Acta* **2009**, *97*, 319–324.

[13] C. Ekberg, E. Aneheim, A. Fermvik, M. Foreman, E. Löfström-Engdahl, T. Retegan, I. Spendlikova, *J. Chem. Eng. Data* **2010**, *55*, 5133–5137.

[14] S. Trumm, A. Geist, P. J. Panak, T. Fanghänel, *Solvent Extr. Ion Exch.* **2011**, *29*, 213–229.

[15] a) C. Musikas, W. Schultz, J.-O. Liljenzin in *Solvent Extraction Principles and Practice*, 2nd ed; (Eds.: J. Rydberg, M. Cox, C. Musikas, G. Choppin), Marcel Dekker Inc., New York, **2004**, pp 507–557; b) K. L. Nash, C. Madic, J. Mathur, J. Lacquement in *The Chemistry of the Actinide and Transactinide Elements*, 3rd ed; (Eds.: L. R. Morss, N. M. Edelstein, J. Fuger, J. J. Katz), Springer, Dordrecht, **2006**, pp 2622–2798.

[16] a) H. Kanno, J. Yamamoto, S. Murahashi, S. Utsuno, J. Fujita, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2936–2941; b) C. P. Horwitz, Q. Zuo, *Inorg. Chem.* **1992**, *31*, 1607–1613; c) H. Kanno, K. Iijima, *Acta. Cryst.* **1997**, *C53*, 498–499; d) R. S. Ward, D. Branciard, R. A. Dignan, M. C. Pritchard, *Heterocycles* **2002**, *56*, 157–170.

[17] P. N. W. Baxter, J. A. Connor, W. B. Schweizer, J. D. Wallis, *J. Chem. Soc. Dalton Trans.* **1992**, 3015–3019.

[18] a) H. E. Katz, *J. Org. Chem.* **1985**, *50*, 2086–2091; b) P. Ferreira, W.-M. Xue, E. Bencze, E. Herdtweck, F. E. Kühn, *Inorg. Chem.* **2001**, *40*, 5834–5841.

[19] J. Stanek, G. Caravatti, H. G. Capraro, J. Frei, EP495749 A1 (**1992**).

[20] a) P. Jones, G. B. Villeneuve, C. Fei, J. DeMarte, A. J. Haggarty, K. T. Nwe, D. A. Martin, A.-M. Lebuis, J. M. Finkelstein, B. J. Gour-Salin, T. H. Chan, B. R. Leyland Jones, *J. Med. Chem.* **1998**, *41*, 3062–3077; b) K. Kikuchi, S. Hibi, H. Yoshimura, N. Tokuhara, K. Tai, T. Hida, T. Yamauchi, M. Nagai, *J. Med. Chem.* **2000**, *43*, 409–419.

[21] F. W. Lewis, L. M. Harwood, M. J. Hudson, WO2011077081 (**2011**).

[22] a) G. R. Pabst, J. Sauer, *Tetrahedron Lett.* **1998**, *39*, 6687–6690; b) G. R. Pabst, O. C. Pfüller, J. Sauer, *Tetrahedron* **1999**, *55*, 5047–5066; c) G. R. Pabst, J. Sauer, *Tetrahedron* **1999**, *55*, 5067–5088.

[23] a) J. Strating, S. Reiffers, H. Wynberg, *Synthesis* **1971**, 209–211; b) R. Isaksson, T. Liljefors, *J. Chem. Soc. Perkin Trans. 2* **1983**, 1351–1356.

[24] J. Kooi, H. Wynberg, R. M. Kellogg, *Tetrahedron* **1973**, *29*, 2135–2140.

[25] a) P. Y. Johnson, J. Zitsman, C. E. Hatch, *J. Org. Chem.* **1973**, *38*, 4087–4089; b) E. L. Clennan, D. R. Speth, P. D. Bartlett, *J. Org. Chem.* **1983**, *48*, 1246–1250.

[26] a) H. Wynberg, A. De Groot, *Chem. Comm.* **1965**, 171–171; b) A. De Groot, H. Wynberg, *J. Org. Chem.* **1966**, *31*, 3954–3958; c) R. F. Evans, K. N. Mewett, *Aust. J. Chem.* **1972**, *25*, 2671–2685.

[27] J. L. Greene Jr., H. J. Hagemeyer Jr., *J. Am. Chem. Soc.* **1955**, *77*, 3016–3018.

[28] F. W. Lewis, L. M. Harwood, M. J. Hudson, M. G. B. Drew, G. Modolo, M. Sypula, J. F. Desreux, N. Bouslimani, G. Vidick, *Dalton Trans.* **2010**, *39*, 5172–5182.

[29] C. Ekberg, I. Dubois, A. Fermvik, T. Retegan, G. Skarnemark, M. G. B. Drew, M. R. S. Foreman, M. J. Hudson, *Solvent Extr. Ion Exch.* **2007**, *25*, 603–617.

[30] For some recent examples with lanthanide salts, see: a) L. N. Puntus, A.-S. Chauvin, S. Varbanov, J.-C. G. Bunzli, *Eur. J. Inorg. Chem.* **2007**, 2315–2326; b) G. Pompidor, A. D'Aleo, J. Vicat, L. Toupet, N. Giraud, R. Kahn, O. Maury, *Angew. Chem. Int. Ed.* **2008**, *47*, 3388–3391; c) P. M. Marcos, J. R. Ascenso, M. A. P. Segurado, R. J. Bernardino, P. J. Cragg, *Tetrahedron* **2009**, *65*, 496–503; d) B. El Aroussi, N. Dupont, G. Bernardinelli, J. Hamacek, *Inorg. Chem.* **2010**, *49*, 606–615; e) P. M. Marcos, J. R. Ascenso, M. A. P. Segurado, P. J. Cragg, S. Michel, V. Hubscher-Bruder, F. Arnaud-Neu, *Supramol. Chem.* **2011**, *23*, 93–101.

[31] For a similar study on BTBP ligands, see: T. Retegan, L. Berthon, C. Ekberg, A. Fermvik, G. Skarnemark, N. Zorz, *Solvent Extr. Ion Exch.* **2009**, *27*, 663–682.

[32] For a review on stability constant determination by NMR and other means, see: P. Thordarson, *Chem. Soc. Rev.* **2011**, *40*, 1305–1323.

[33] D. Serrano-Purroy, P. Baron, B. Christiansen, R. Malmbeck, C. Sorel, J.-P. Glatz, *Radiochim. Acta* **2005**, *93*, 351–355.

[34] a) G. Modolo, H. Asp, C. Schreinemachers, H. Vijgen, *Solvent Extr. Ion Exch.* **2007**, *25*, 703–721; b) D. Magnusson, B. Christiansen, J.-P. Glatz, R. Malmbeck, G. Modolo, D. Serrano-Purroy, C. Sorel, *Solvent Extr. Ion Exch.* **2009**, *27*, 26–35.

[35] a) M. Nilsson, S. Andersson, F. Drouet, C. Ekberg, M. Foreman, M. Hudson, J.-O. Liljenzin, D. Magnusson, G. Skarnemark, *Solvent Extr. Ion Exch.* **2006**, *24*, 299–318; b) M. Nilsson, C. Ekberg, M. Foreman, M. Hudson, J.-O. Liljenzin, G. Modolo, G. Skarnemark, *Solvent Extr. Ion Exch.* **2006**, *24*, 823–843; c) T. Retegan, C. Ekberg, I. Dubois, A. Fermvik, G. Skarnemark, T. Johnsson Wass, *Solvent Extr. Ion Exch.* **2007**, *25*, 417–431.

[36] L. M. Harwood, F. W. Lewis, M. J. Hudson, J. John, P. Distler, *Solvent Extr. Ion Exch.* **2011**, *29*, 551–576.

[37] See for example: a) C. Hill, D. Guillaneux, L. Berthon, C. Madic, *J. Nucl. Sci. Technol.* **2002**, (*Supp 3*), 309–312; b) A. Fermvik, L. Berthon, C. Ekberg, S. Englund, T. Retegan, N. Zorz, *Dalton Trans.* **2009**, 6421–6430.

[38] a) N. Feeder, M. J. Ginnelly, R. V. H. Jones, S. O'Sullivan, S. Warren, *Tetrahedron Lett.* **1994**, *35*, 9095–9098; b) N. Feeder, M. J. Ginnelly, R. V. H. Jones, S. O'Sullivan, S. Warren, P. Wyatt, *J. Chem. Soc. Perkin Trans. 1* **1997**, 3479–3483.

[39] Although we have used carbon tetrachloride in the present procedure, we have shown during the synthesis of diketone **11** that carbon tetrachloride can be replaced with DCM in these reactions; see refs. 11 and 21.

[40] K. Ebert, H. Ederer, *Computeranwendungen in der Chemie*, Wiley-VCH Verlagsgesellschaft mbH, Weinheim, **1985**.

[41] A. L. Herbelin, J. C. Westall, *FITEQL – A Computer Program for Determination of Chemical Equilibrium Constants from Experimental Data*, Version 3.2., Report 94-01, Department of Chemistry, Oregon State University, Corvallis, Oregon, **1996**.

[42] L. Dvořák, M. Ledvinka, M. Sobotka, *FAMULUS 3.1*, Computer Equipment, Prague, **1991**.

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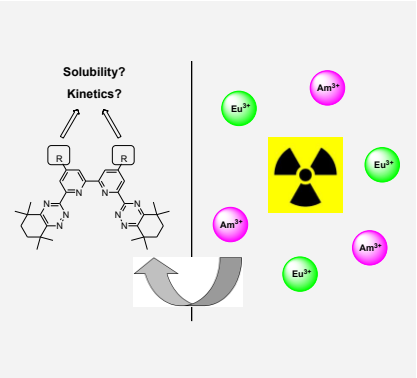
Entry for the Table of Contents

Layout 1:

Actinide Partitioning

Four lipophilic alkyl-substituted 6,6'-bis(1,2,4-triazin-3-yl)-2,2'-bipyridine (BTBP) ligands have been synthesized and the effects of additional alkyl substitution on their extraction properties in nuclear waste treatment have been studied by Am(III)/Eu(III) solvent extraction experiments and lanthanide NMR titrations.

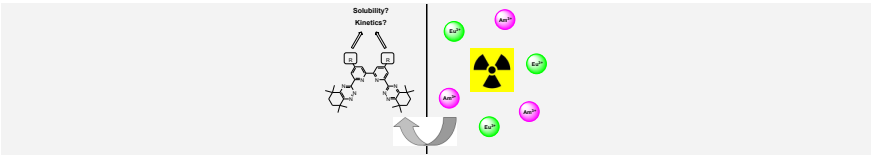


Frank W. Lewis,* Laurence M. Harwood,* Michael J. Hudson, Petr Distler, Jan John, Karel Stamberg, Ana Nuñez, Hitos Galan and Amparo G. Espartero…….. Page No. – Page No.

Synthesis and Evaluation of Lipophilic BTBP Ligands: Effect of Alkyl Substitution on Extraction Properties and Implications for Ligand Design

Layout 2:

Actinide Partitioning



Four lipophilic alkyl-substituted 6,6'-bis(1,2,4-triazin-3-yl)-2,2'-bipyridine (BTBP) ligands have been synthesized and the effects of additional alkyl substitution on their extraction properties in nuclear waste treatment have been studied by Am(III)/Eu(III) solvent extraction experiments and lanthanide NMR titrations.

Frank W. Lewis,* Laurence M. Harwood,* Michael J. Hudson, Petr Distler, Jan John, Karel Stamberg, Ana Nuñez, Hitos Galan and Amparo G. Espartero ……... Page No. – Page No.

Synthesis and Evaluation of Lipophilic BTBP Ligands: Effect of Alkyl Substitution on Extraction Properties and Implications for Ligand Design

Supporting Information

Electronic Supplementary Information

for the paper entitled

Synthesis and Evaluation of Lipophilic BTBP Ligands for An/Ln Separations in Nuclear Waste Treatment: Effect of Alkyl Substitution on Extraction Properties and Implications for Ligand Design

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CONTENTS **PAGE**

1. NMR Titrations with Lanthanide Salts

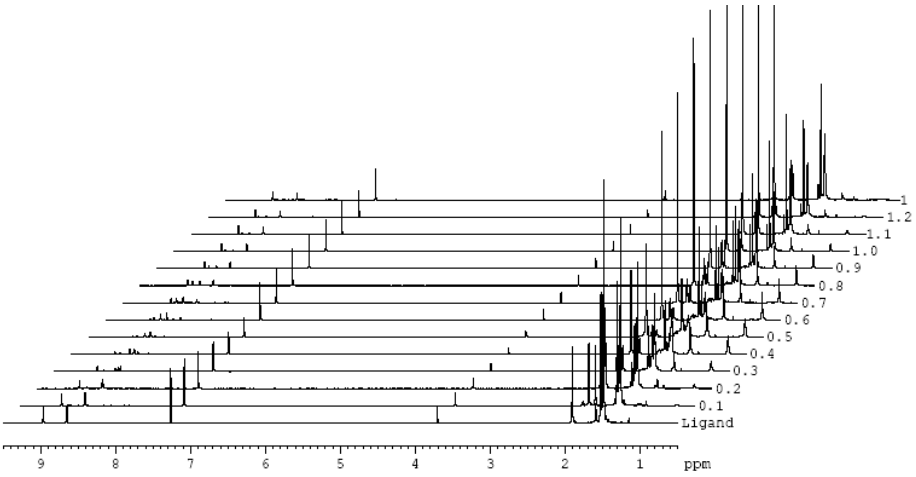

Figure 1. Stack plot for the ^{1}H NMR titration of BTBP **13** with $La(NO_3)_3$. First (bottom) spectrum = free ligand. Each subsequent spectrum corresponds to the addition of 0.1 eq. of $La(NO_3)_3$.

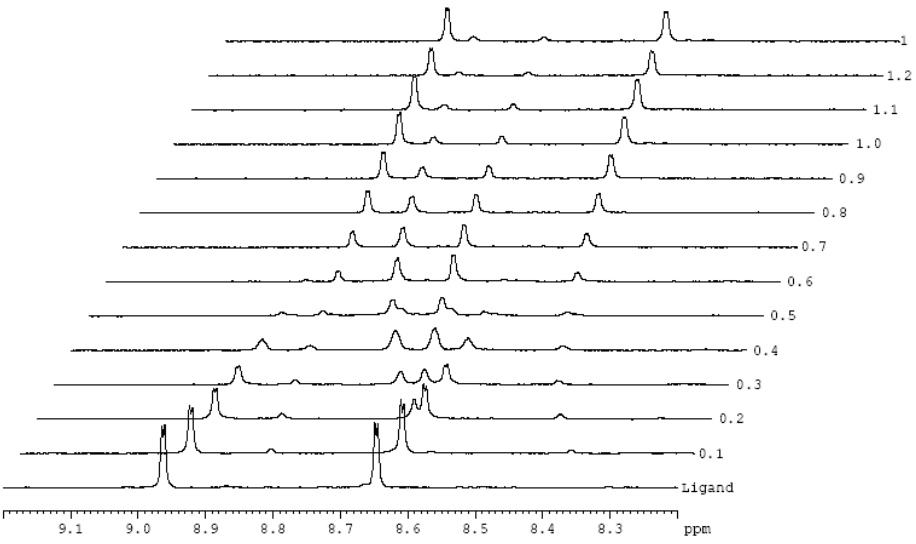

Figure 2. Enlargement of the aromatic region of the stack plot for the ^{1}H NMR titration of BTBP **13** with $La(NO_3)_3$. First (bottom) spectrum = free ligand. Each subsequent spectrum corresponds to the addition of 0.1 eq. of $La(NO_3)_3$.

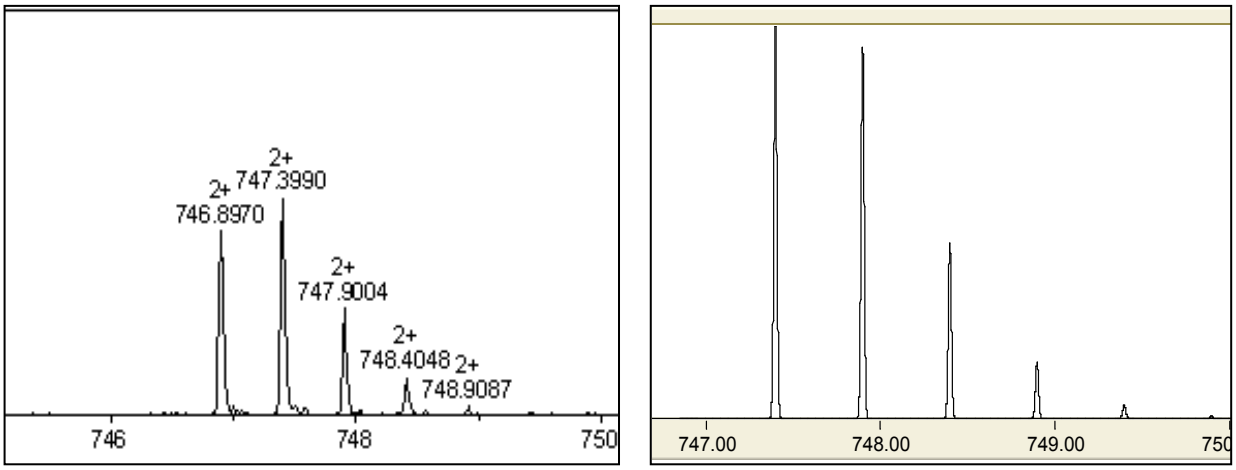

Figure 3. Left: Enlargement of the electrospray-ionization mass spectrum of the final solution species formed during the titration of BTBP **13** with $La(NO_3)_3$. The mass peak at m/z = 746.8970 corresponds to $[La(\mathbf{13})_2(NO_3)]^{2+}$. Right: Computer simulation of the isotope distribution pattern of $[La(\mathbf{13})_2(NO_3)]^{2+}$.

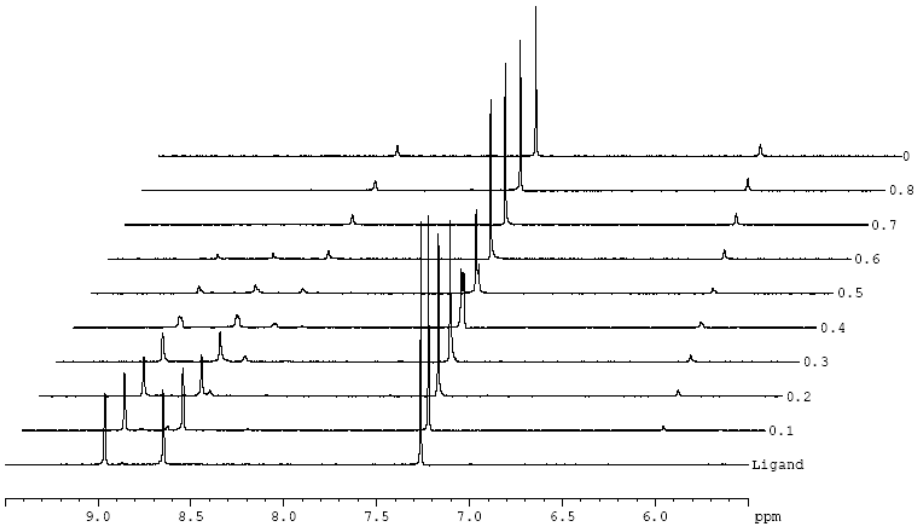

Figure 4. Enlargement of the aromatic region of the stack plot for the ^{1}H NMR titration of BTBP **13** with $Eu(NO_3)_3$. First (bottom) spectrum = free ligand. Each subsequent spectrum corresponds to the addition of 0.1 eq. of $Eu(NO_3)_3$. Peak at 7.26 ppm = $CHCl_3$.

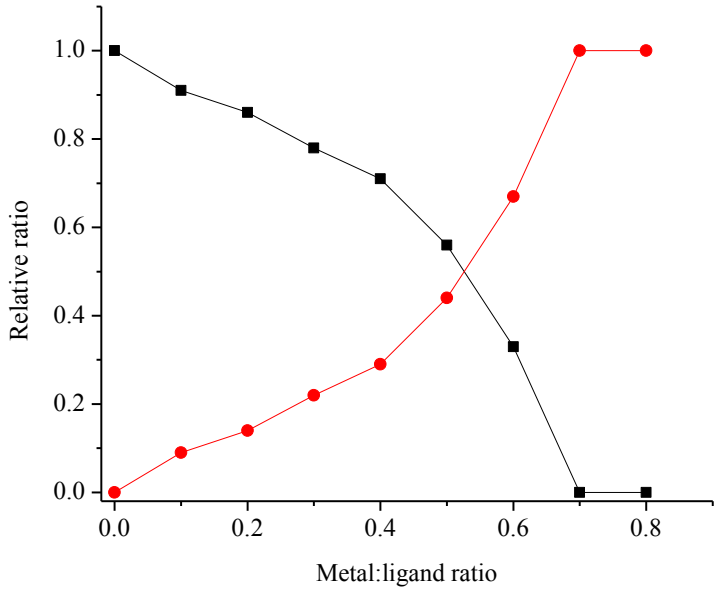

Figure 5. ^{1}H NMR titration of BTBP **13** with $Eu(NO_3)_3$ (■ = free ligand, ● = 1:2 complex).

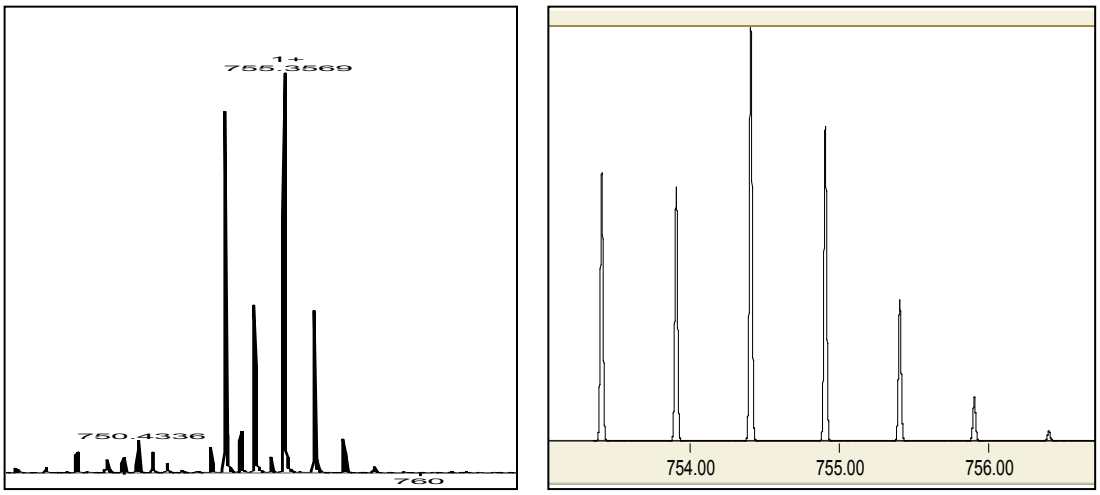

Figure 6. Left: Enlargement of the electrospray-ionization mass spectrum of the final solution species formed during the titration of BTBP **13** with $Eu(NO_3)_3$. The mass peak at m/z = 755.3569 corresponds to $[Eu(\mathbf{13})_2(NO_3)]^{2+}$. Right: Computer simulation of the isotope distribution pattern of $[Eu(\mathbf{13})_2(NO_3)]^{2+}$.

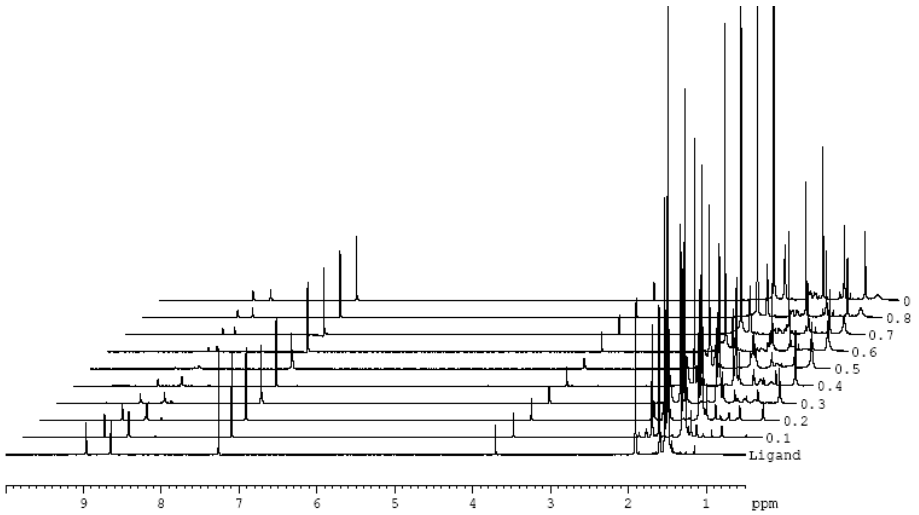

Figure 7. Stack plot for the ^{1}H NMR titration of BTBP **13** with $Ce(NO_3)_3$. First (bottom) spectrum = free ligand. Each subsequent spectrum corresponds to the addition of 0.1 eq. of $Ce(NO_3)_3$.

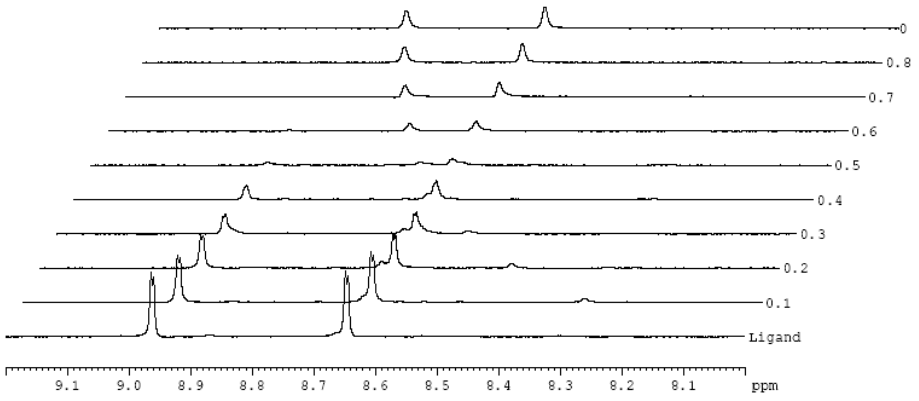

Figure 8. Enlargement of the aromatic region of the stack plot for the ^{1}H NMR titration of BTBP **13** with $Ce(NO_3)_3$. First (bottom) spectrum = free ligand. Each subsequent spectrum corresponds to the addition of 0.1 eq. of $Ce(NO_3)_3$.

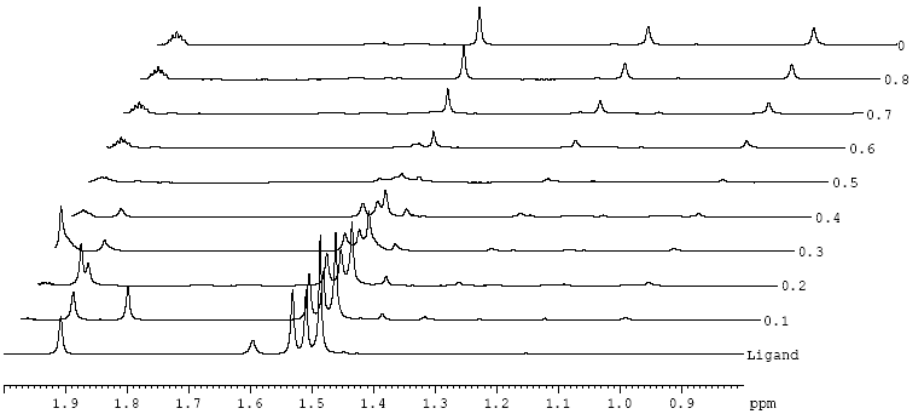

Figure 9. Enlargement of the aliphatic region of the stack plot for the ^{1}H NMR titration of BTBP **13** with $Ce(NO_3)_3$. First (bottom) spectrum = free ligand. Each subsequent spectrum corresponds to the addition of 0.1 eq. of $Ce(NO_3)_3$.

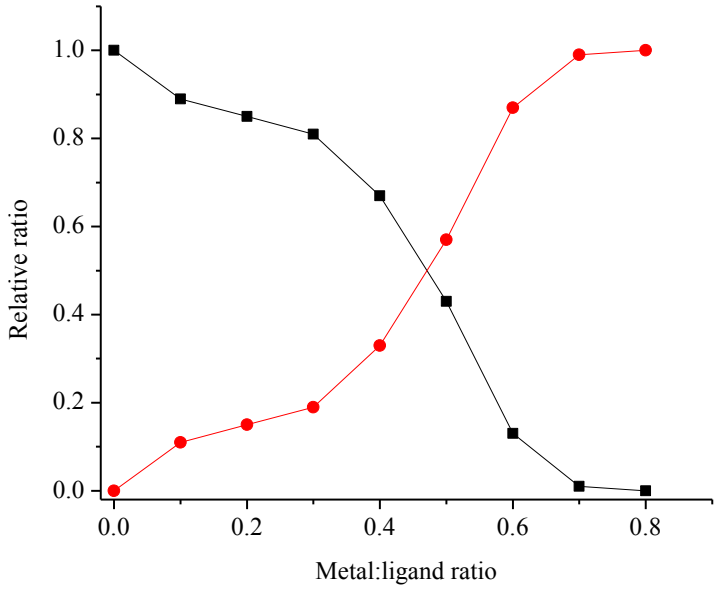

Figure 10. ^{1}H NMR titration of BTBP **13** with $Ce(NO_3)_3$ (■ = free ligand, ● = 1:2 complex).

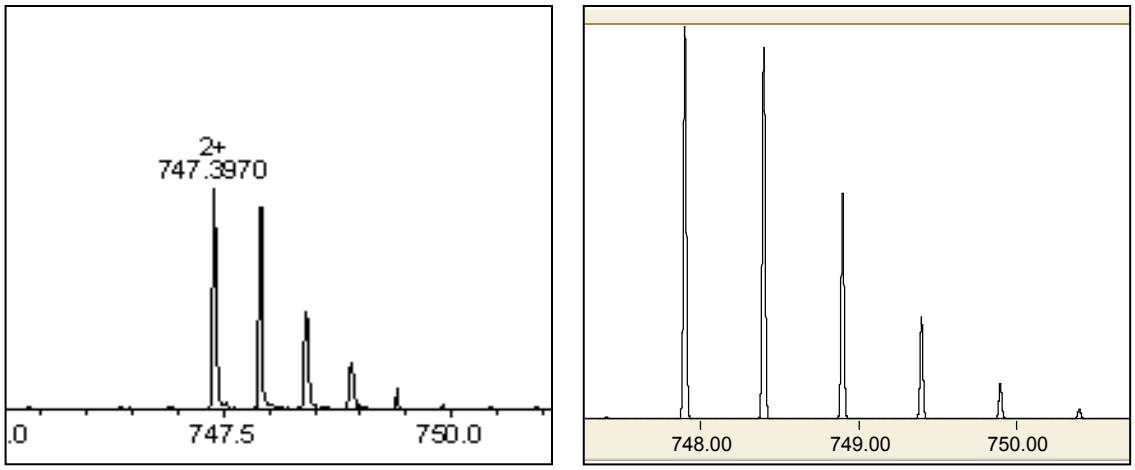

Figure 11. Left: Enlargement of the electrospray-ionization mass spectrum of the final solution species formed during the titration of BTBP **13** with $Ce(NO_3)_3$. The mass peak at m/z = 747.3970 corresponds to $[Ce(\mathbf{13})_2(NO_3)]^{2+}$. Right: Computer simulation of the isotope distribution pattern of $[Ce(\mathbf{13})_2(NO_3)]^{2+}$.

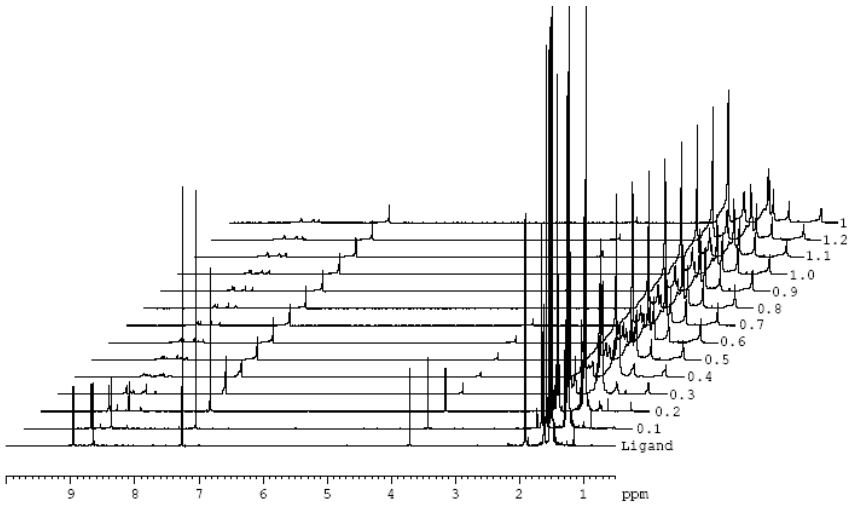

Figure 12. Stack plot for the ^{1}H NMR titration of BTBP **13** with $Y(NO_3)_3$. First (bottom) spectrum = free ligand. Each subsequent spectrum corresponds to the addition of 0.1 eq. of $Y(NO_3)_3$.

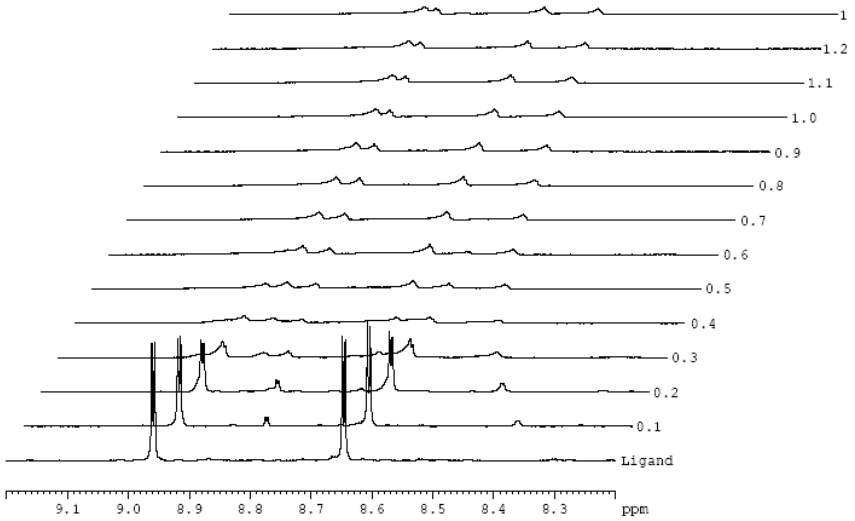

Figure 13. Enlargement of the aromatic region of the stack plot for the ^{1}H NMR titration of BTBP **13** with $Y(NO_3)_3$. First (bottom) spectrum = free ligand. Each subsequent spectrum corresponds to the addition of 0.1 eq. of $Y(NO_3)_3$.

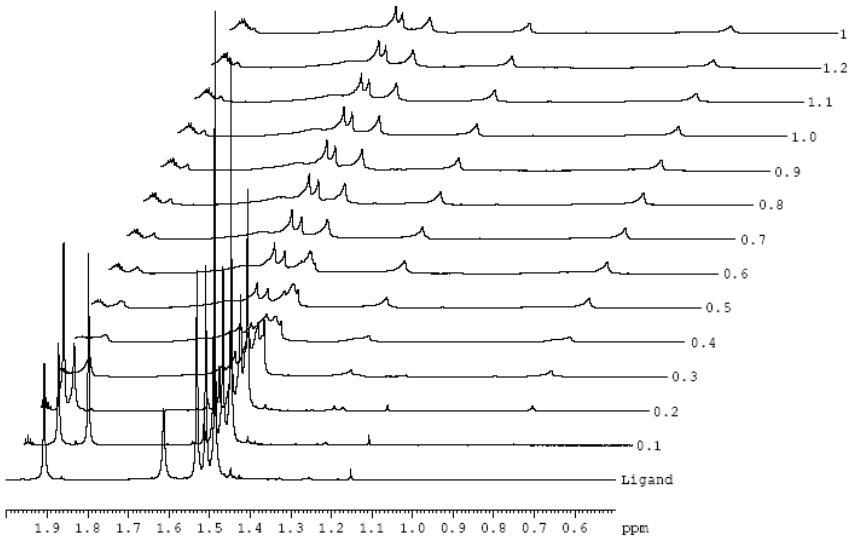

Figure 14. Enlargement of the aliphatic region of the stack plot for the ^{1}H NMR titration of BTBP **13** with $Y(NO_3)_3$. First (bottom) spectrum = free ligand. Each subsequent spectrum corresponds to the addition of 0.1 eq. of $Y(NO_3)_3$.

2. Calculation of Stability Constants

General procedure

The data resulting from the ^{1}H NMR titrations of BTBP **13** with nitrate salts of Ce(III), Eu(III), La(III) and Y(III) were used for the modelling of the complexation reactions with the aim of obtaining the values of the stability constants. In the course of the titrations, successive increments of metal ions were added into the NMR tube containing a known amount of ligand **13**. Two or three species, as a function of metal/ligand ratio, were detected by means of NMR measurements, namely, free ligand (BTBP) and 1:2 complex (M:2 BTBP) in the case of Eu(III) and Ce(III) salts, or free ligand, 1:1 complex (M:BTBP) and 1:2 complex (M:2 BTBP) in the case of La(III) and Y(III) salts. One or two stability constants (K), corresponding to the complexes mentioned, were thus sought. The primary experimental data were expressed in the form of "normalized relative integrations (i.e.: species distribution)", $(x_i) = L_x/L_0$, $(y_i) = L_y/L_0$, $(z_i) = L_z/L_0$, where L_0, L_x, L_y, *and* L_z are integrated NMR signals for the initial amount of ligand, free ligand, and the ligand bound in 1:1, or 1:2 complexes, respectively. The dimensions of these "normalized relative integrations" are "molar fraction" of the given species (each fraction being expressed relative to the initial amount of substance of the ligand). It is evident that such primary data cannot be used directly as input data in the modelling procedure because the stability constant is a function of molar concentrations (mol/L) of individual components (species) taking part in the complexation reaction. Therefore, in the first step of the modelling study, the primary experimental data were rectified, then the complexation model was proposed and the corresponding code was constructed and, in the last step, the stability constants were calculated.

The rectification of the primary experimental data

The parameters of the titration experiments:

L_0 = 5e-6 mole (initial amount of substance of the ligand in NMR tube in V_0); V_0 = 0.5 mL; $(\Delta V)_i$ = 0.05 mL (solution of 5e-7 moles of metal salt added to V_0 at each i-th titration point); $(V\Sigma)_i \in$<0.5;1.15> mL (total volume in the NMR tube at the i-th titration point); $(M_0)_i/L_0 \in$ <0;0.8> mL (value of molar metal/ligand ratio at each i-th titration point); $(x_i) \in$<0;1> mL (molar fraction of free ligand, relative to L_0), $(y_i) \in$ <0;1> mL (molar fraction of complex 1:1, relative to L_0); $(z_i) \in$ <0;1> mL (molar fraction of complex 1:2, relative to L_0).

Calculation of molar concentrations (for i-th titration point):

$(CM\Sigma)_i = ((M_0)_i/L_0) \cdot L_0/1000/(V\Sigma)_i$ ….. total concentration of metal, mol M/L;

$(CL_0)_i = (L_0/1000/(V\Sigma)_i)$ ….. total concentration of ligand, mol BTBP/L;

$(CMx)_i = ((((M_0)_i/L_0) \cdot L_0) - (y_i) \cdot L_0) - (z_i)/2 \cdot L_0))/1000/(V\Sigma)_i$ ... concentration of metal free, mol M/L;

$(CLx)_i = ((x_i) \cdot L_0/1000/(V\Sigma)_i)$ …. concentration of ligand free, mol BTBP/L;

$(CLy)_i = ((y_i) \cdot L_0/1000/(V\Sigma)_l$ ….. concentration of 1:1 complex, mol BTBP/L = mol M/L;

$(CLz)_i = ((z_i) \cdot L_0/1000/(V\Sigma)_l$ ….. concentration of 1:2 complex, mol BTBP/L = 2 mol M/L.

Model describing the complexation reactions and its solution

The model used was defined as two complexation reactions taking place in the systems studied:

$$M + L \leftrightarrow ML \qquad K1 = [ML] / ([M]\,[L]) \qquad (1)$$

$$M + 2\,L \leftrightarrow ML_2 \qquad K2 = [ML_2] / ([M]\,[L]^2) \qquad (2)$$

Where equations (1) and (2) are relations defining the stability (equilibrium) constants *K1* and *K2* for the formation of the 1:1 and 1:2 complexes, respectively.

The definitions of the symbols are:

[M] … equilibrium molar concentration of free metal (=$(CMx)_i$);

[L] … equilibrium molar concentration of free ligand (=$(CLx)_i$);

[ML] .. equilibrium molar concentration of 1:1 complex (=$(CLy)_i$);

[ML_2] .. equilibrium molar concentration of 1:2 complex (=2 $(CLz)_i$)

Then, the following balanced equations, namely for ligand (3) and metal (4), hold:

$$(CL_0)_i = (CLx)_i + (CLy)_i + (CLz)_i \qquad (3)$$

$$(CM\Sigma)_i = (CMx)_i + (CLy)i + 2\,(CLz)_i \qquad (4)$$

If the expressions (1) and (2) are inserted into balanced equations (3) and (4), then two basic model equations (5) and (6), which are the substance of the so called regression function, are obtained after their arrangement, namely:

- for ligand free concentration (quadratic equation):

$$0 = (CLx)_i - \{(CL_0)_i - [(CM\Sigma)_i / (1 + K1 \cdot (CLx)_i) + K2 \cdot (CLx)_i)^2)] \cdot (K1 \cdot (CLx)_i) + 2 \cdot K2 \cdot (CLx)_i)^2)\} \qquad (5)$$

- for metal free concentration:

$$(CMx)_i = (CM\Sigma)_i / (1 + K1 \cdot (CLx)_i) + K2 \cdot (CLx)_i)^2) \qquad (6)$$

It is evident that these equations have to be solved in iteration cycle by a non-linear regression procedure in the course of which the experimentally determined (and rectified) data are fitted with the data calculated by equations (1), (2), (5) and (6). The Newton Raphson multidimensional non-linear regression procedure was used and the values of the stability constants, *K1* and *K2*, were sought.

The fitting, as mentioned above, proceeds in the iteration cycle from which it is possible to withdraw the parameters sought when the difference of the sum of relative squares of deviations $(SSx)_j$ after two successive cycles (i.e., j^{th} and j^{th+1}) is less than 10^{-8} (eq. (7)):

$$(SSx)_j = \Sigma((A_{rel,cal} - A_{rel,exp})_j/(A_{rel,exp})_j)^2 \qquad (7)$$

The respective computational code PMeBTBP1.fm (Code Package Stamb-2011) is constructed from the FAMULUS software product, which is used for all the calculations. As the fitting criterion, reflecting the agreement between calculated and experimental values, the chi-square (χ^2), defined by eq. (8), is used and subsequently, the *WSOS/DF* (Weighted Sum Of Squares divided by the Degrees of Freedom) quantity is calculated by eq. (9).

$$\chi^2 = \sum_{i=1}^{N} \frac{(SSx)_i}{(s_q)_i^2} \tag{8}$$

$$WSOS/DF = \frac{\chi^2}{n_i - n} \tag{9}$$

where: s_q = standard uncertainty of experimental determination of $A_{rel,exp}$; N, n_p = overall number of experimental points; n_i = number of degrees of freedom; n = number of searched parameters (in our case n = 1 or 2). Generally, the agreement is acceptable if $0.1 \leq WSOS/DF \leq 20$.

Results and discussion

The results are demonstrated in Figure 14 for the system Ce – BTBP and in Figure 15 for the system Y – BTBP. In the first case only one stability constant (K) was sought, while two constants were sought in the second case.

If we take into account the value of WSOS/DF (1.47), the result of the Ce – BTBP system modelling seems to be acceptable. On the other hand, the graphical evaluation in Figure 14 does not look as optimistic. These results indicate that the first complexation reaction probably proceeds in this system, too, especially if the metal/ligand ratio is greater than 0.30 (It could be possible to study, or to predict such a complex, by modifying the present model). However, it should be noted that this second complex was not detected by NMR analysis.

As for the system Y – BTBP, it is necessary to note that some difficulties existed already in the first step of this study, namely, some of the metal free concentrations calculated were lower than zero. Most probably, this effect has been caused by the superposition of the experimental uncertainties in the calculation. Hence, careful attention should be paid to this type of system, both in the course of experiments, and during the evaluation. The results obtained for Eu and La and their discussion are similar to those discussed above for Ce and Y.

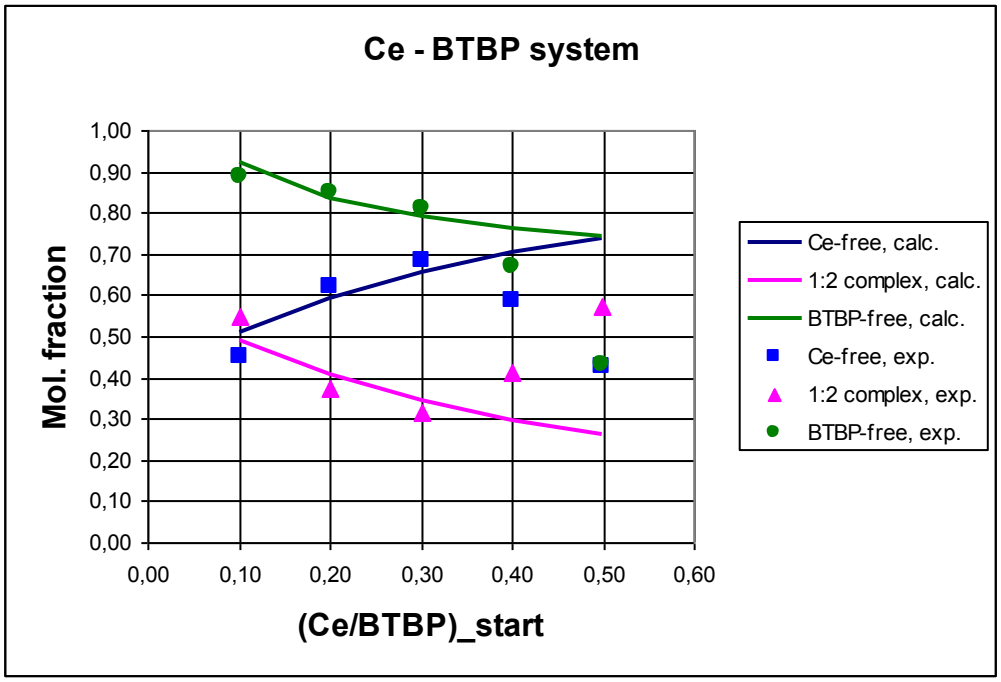

Figure 15.

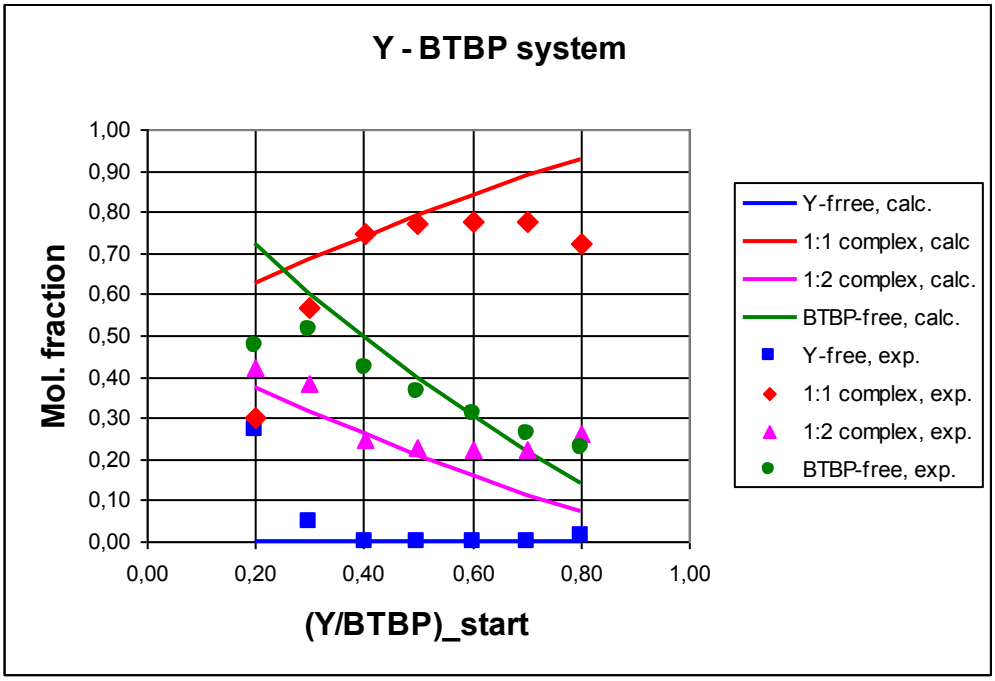

Figure 16.

3. Solvent Extraction Properties

Table 1. Extraction of Am(III) and Eu(III) into 1-octanol by BTBP ligands **12** and **13** (5 mM for **12**, 4.8 mM for **13**) as a function of [HNO_3], contact time = 6 hours at 25 °C, non-thermostatted

[HNO_3] Initial (mol/L)	BTBP **12**			BTBP **13**		
	D_{Am}	D_{Eu}	$SF_{Am/Eu}$	D_{Am}	D_{Eu}	$SF_{Am/Eu}$
0.01	0.007	< 0.003	> 2.3	–[a]	–[a]	–[a]
0.1	0.040	< 0.003	> 13.5	0.002	0.003	1
0.5	0.156	0.012	13.0	0.041	0.004	10.3
1	0.323	0.024	13.5	0.109	0.016	6.8
2	0.610	0.028	21.8	0.186	0.019	9.8
4	0.572	0.022	26.0	0.621	0.042	14.8

[a] Not measured.

Table 2. Extraction of Am(III) and Eu(III) into cyclohexanone by BTBP ligands **12** and **13** (5 mM) as a function of [HNO_3], contact time = 6 hours at 25 °C, non-thermostatted

[HNO_3] Initial (mol/L)	BTBP **12**			BTBP **13**		
	D_{Am}	D_{Eu}	$SF_{Am/Eu}$	D_{Am}	D_{Eu}	$SF_{Am/Eu}$
0.01	0.4	0.006	59.0	–[a]	–[a]	–[a]
0.1	1.2	0.025	46.4	0.189	0.008	23.6
0.5	20.4	0.125	163.5	6.3	0.067	93.4
1	15.6	0.104	150.1	23.2	0.204	113.9
2	27.6	0.212	130.2	40.7	0.43	94.7
3	–[a]	–[a]	–[a]	51.4	0.529	97.2
4	13.8	0.122	113.0	–[a]	–[a]	–[a]

[a] Not measured.

Table 3. Extraction of Am(III) into 1-octanol from 4 M HNO_3 by BTBPs **12** and **13** (5 mM for **12**, 4.8 mM for **13**) as a function of contact time at 25 ^{o}C, non-thermostatted

Contact time (h)	D_{Am} for BTBP **12**	D_{Am} for BTBP **13**
2	0.292	0.083
4	0.547	0.137
6	0.572	0.285
18	1.301	0.954
30	2.33	1.756

Table 4. Extraction of Am(III) into cyclohexanone from 2 M HNO_3 by BTBPs **12** and **13** (5 mM) as a function of contact time at 25 ^{o}C, non-thermostatted

Contact time (min)	D_{Am} for BTBP **12**	D_{Am} for BTBP **13**
5	5.4	0.796
10	11.1	1.44
20	27.6	3.33
30	32.3	6.23
45	31.1	9.95
60	31.5	19.7
90	29.7	31.8
120	29.0	39.8
360	27.6	40.7

Table 5. Extraction of Am(III) and Eu(III) into 3-methylcyclohexanone by BTBP ligand **12** (5 mM) as a function of [HNO_3], contact time = 6 hours at 25 ^{o}C, non-thermostatted

[HNO_3] Initial (mol/L)	D_{Am}	D_{Eu}	$SF_{Am/Eu}$
0.01	0.008	0.006	1.3
0.1	0.027	0.006	9
0.5	0.13	0.005	26
1	0.239	0.024	19
2	0.207	0.028	7.4
4	0.206	0.021	9.8

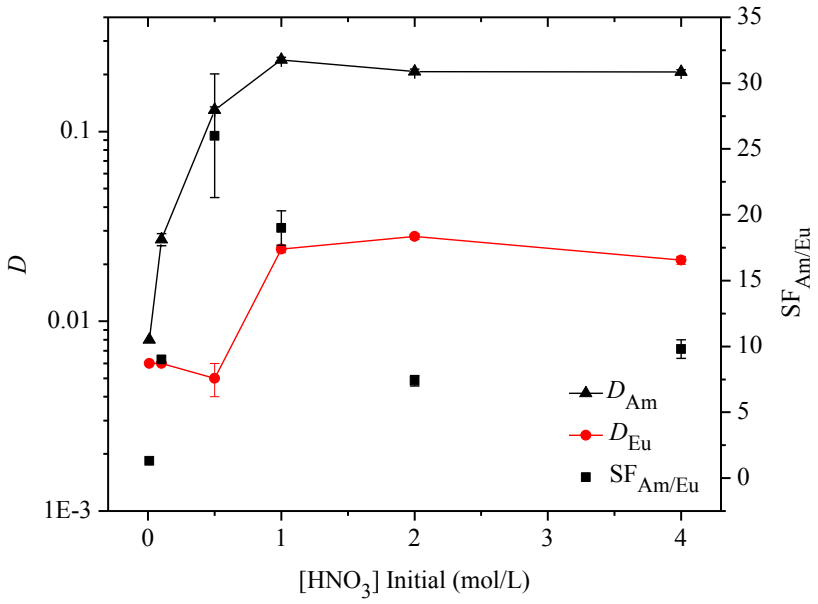

Figure 17. Extraction of Am(III) and Eu(III) as a function of [HNO_3] for BTBP **12** in 3-methylcyclohexanone (5 mM) at 25 °C, non-thermostatted (▲ = D_{Am}, ● = D_{Eu}, ■ = $SF_{Am/Eu}$, contact time = 6 hours).

Table 6. Extraction of Am(III) and Eu(III) into 1-octanol by BTBP **13** (10 mM) as a function of contact time at three different aqueous phase acidities

Contact time (min)	0.2 M HNO_3[a]		1 M HNO_3[b]		3 M HNO_3[c]	
	D_{Am}	D_{Eu}	D_{Am}	D_{Eu}	D_{Am}	D_{Eu}
5	0.00769	0.0007	0.0627	0.00407	0.119	0.00865
15	0.0193	0.00102	0.211	0.0113	0.335	0.0199
30	0.0373	0.00142	0.420	0.0195	0.605	0.0304
45	0.0485	0.00193	0.531	0.0231	0.959	0.0383
60	0.0568	0.00214	0.654	0.0319	1.35	0.0487
75	0.0649	0.00269	0.817	0.0346	1.80	0.0586
90	0.0646	0.00282	0.946	0.0443	2.75	0.0874

[a] At 22 °C. [b] At 20–22 °C. [c] At 18–20 °C.

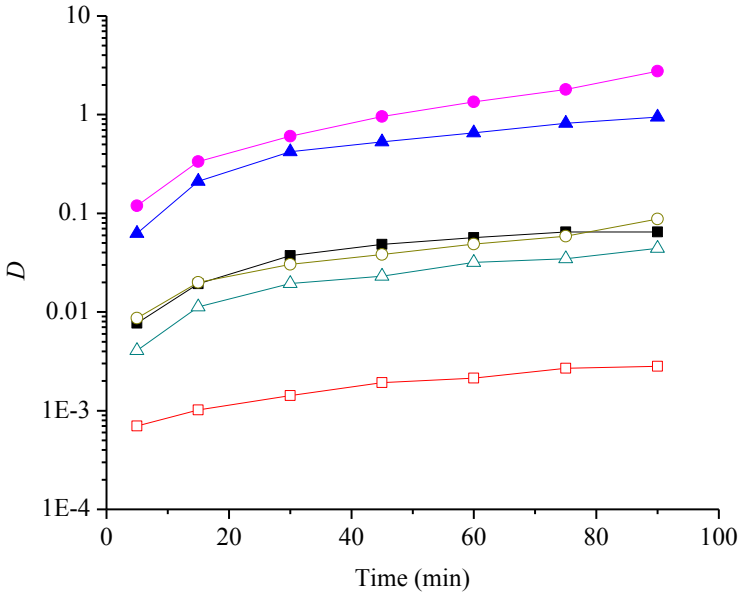

Figure 18. Extraction of Am(III) and Eu(III) into 1-octanol by BTBP **13** (10 mM) as a function of contact time at three different aqueous phase acidities (■ = D_{Am} at 0.2 M HNO_3, □ = D_{Eu} at 0.2 M HNO_3, ▲ = D_{Am} at 1 M HNO_3, Δ = D_{Eu} at 1 M HNO_3, ● = D_{Am} at 3 M HNO_3, ○ = D_{Eu} at 3 M HNO_3).

Table 7. Extraction of Am(III) and Eu(III) from 3 M HNO_3 into 1-octanol by BTBP **13** (10 mM) as a function of contact time at three different concentrations of the phase modifier DMDOHEMA

Contact time (min)	DMDOHEMA (0.05 M)[a]		DMDOHEMA (0.16 M)[a]		DMDOHEMA (0.25 M)[b]	
	D_{Am}	D_{Eu}	D_{Am}	D_{Eu}	D_{Am}	D_{Eu}
5	0.152	0.0125	0.299	0.0271	0.323	0.0435
10	0.394	0.0230	0.509	0.0436	0.652	0.0626
15	0.580	0.0322	1.15	0.0608	1.04	0.0736
20	0.841	0.0440	1.87	0.0721	1.58	0.0946
30	1.21	0.0576	2.14	0.105	2.47	0.118
45	1.88	0.0712	–[c]	–[c]	3.6	0.155

[a] At 22 °C. [b] At 19 °C. [c] Not measured.

Table 8. Extraction of Am(III) and Eu(III) from 3 M HNO_3 into 1-octanol by BTBP **13** (10 mM) as a function of contact time in the presence of the phase modifier TODGA (0.005 M) at 18 °C

Contact time (min)	D_{Am}	D_{Eu}
5	0.536	0.742
15	1.23	0.81
30	2.24	0.787
45	3.63	0.8
60	6.72	0.984
75	9.23	0.98
90	11.5	0.863

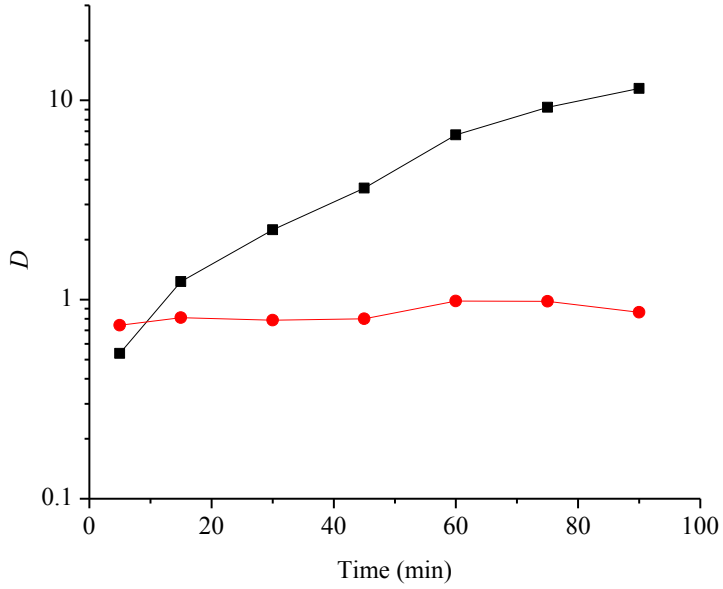

Figure 19. Extraction of Am(III) and Eu(III) from 3 M HNO_3 into 1-octanol by BTBP **13** (10 mM) as a function of contact time in the presence of 0.005 M TODGA (■ = D_{Am}, ● = D_{Eu}).